



UNIVERSITY
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Determinants, correlates and modifiers of musculoskeletal pain

by

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Doctor of Philosophy (Medical Research)

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Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by any other person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Ethical Conduct

“The research associated with this thesis abides by the international and Australian codes on human experimentation, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.”

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved each study, and we obtained written informed consent from all participants. Approval numbers are as follows:

Tasmanian Older Adult Cohort Study (TASOAC): H0006488

A randomised controlled trial of arthritis relief plus for osteoarthritis of the knee (4Jointz study): H10988

Zoledronic acid in knee pain associated with bone marrow oedema (ZAP trial): H0010319

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Statement of authorship

This thesis includes papers for which Laura Laslett (LLL) was not the sole author. LLL was the first author in the research of each manuscript; however, she was assisted by the co-authors whose contributions are detailed below.

Chapter 4

Laslett LL, Quinn SJ, Winzenberg TM, Sanderson K, Cicuttini F, Jones G. A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. BMC Musculoskelet Disord. 2012 Sep 7;13(1):168.

LLL analysed the data, wrote the draft manuscript and completed revisions.

SJQ assisted with data analysis and provided statistical advice.

TW KS and FC contributed to discussions about the underlying patterns of associations.

GJ designed the TASSOAC study, the study from which the data in this manuscript is taken, and formulated the hypotheses for this analysis.

All authors contributed to data interpretation, critically revised the manuscript for important intellectual content, and read and approved the final manuscript.

Chapter 5

Laslett LL, Quinn SJ, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a five year longitudinal study. Ann Rheum Dis. 2013 [epub before print].

LLL analysed the data, wrote the draft manuscript and completed revisions.

SJQ provided statistical advice.

JB and VP contributed expertise and laboratory support for analysis of serum samples for vitamin D metabolites.

TMW contributed epidemiological expertise.

GJ designed and obtained funding for the original TASSOAC study and contributed to the design of specific analyses.

CD formulated the hypotheses for this analysis and contributed to the design of specific analyses.

All authors contributed to data interpretation, critically revised the manuscript for important intellectual content, read and approved the final manuscript.

Chapter 6

Laslett LL, Quinn S, Darian-Smith E, Kwok M, Fedorova T, Körner H, Steels E, March L, Jones G. Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial. Osteoarthritis Cartilage. 2012;20(11):1209-16.

LLL dispensed medication, cleaned and analysed data, wrote the draft manuscript and completed revisions.

SQ provided statistical advice.

ED-S and MK were involved in analysis of data.

TF was involved in acquisition of data.

HK provided technical expertise and advice on the laboratory tests.

LM was involved in the conception and design of the study.

GJ was involved in the conception and design of the study and obtained funding.

LL, SQ, LM, ES and GJ were involved in data interpretation.

All authors were involved in drafting the article or revising it critically for intellectual content, and all authors read and approved the final version to be submitted.

Chapter 7

Laslett LL, Doré DA, Quinn SJ, Boon P, Ryan E, Winzenberg TM, Jones G. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Ann Rheum Dis. 2012 Feb 21;71(8):1322-8.

LLL recruited patients, dispensed medication, cleaned and analysed data, wrote the draft manuscript and completed revisions.

DAD read and interpreted MR images.

SJQ provided statistical advice.

PB recruited and screened patients, and assisted with data collection.

ER assisted with data collection.

GJ designed the study, obtained funding and screened patients.

LLL, DAD, SJQ, TMW and GJ participated in data interpretation.

All authors critically reviewed and edited the manuscript and read and approved the final version.

Appendix

Laslett LL, Just (nee Foley) SJ, Quinn SJ, Winzenberg TM, Jones G. Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study. Osteoporos Int. 2012;23:67-74.

LLL extracted, cleaned and analysed the data, wrote the draft manuscript and completed revisions.

SJJ read the morphometric DXA images.

SJQ provided statistical advice.

TW provided the analysis idea of using a threshold.

GJ designed the TASOAC study, and formulated the hypotheses for this analysis.

LLL, SJQ, TMW and GJ participated in data interpretation.

All authors critically reviewed and edited the manuscript, read and approved the final version.

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Abstract

Arthritis is the most common cause of chronic pain in older people. Pain is a priority for patients and an important clinical symptom, as it predicts service use, disability and joint replacements. Treatment options remain palliative, and effect sizes suboptimal. This thesis investigates correlates, determinants and modifiers of musculoskeletal pain.

The first study utilised data from TASSOAC, a population of community dwelling older adults aged 50–80 randomly selected from the electoral roll and followed for five years to describe associations between aspects of osteoarthritis (OA) and quality of life. This study identified that pain at all joint sites is common in older adults, is stable over time, and is the strongest musculoskeletal correlate of quality of life. Pain also mediates the association between diagnosed OA and quality of life.

In the second study, in this same population, associations between serum vitamin D (25–OHD) and change in knee and hip pain were investigated. Moderate (but not mild) vitamin D deficiency independently predicted incident or worsening in knee pain over 5 years and possibly hip pain over 2.4 years. Therefore correcting moderate vitamin deficiency may attenuate worsening of knee or hip pain in elderly persons but supplementing people with a higher 25–OHD level is unlikely to be effective.

In the third and fourth studies, potential modifiers of musculoskeletal pain were investigated. In the former, efficacy of thrice daily topical 4Jointz utilizing Acteev technology (a combination of a standardized comfrey extract and pharmaceutical grade tannic acid, 3.5 g/day) vs placebo was assessed on osteoarthritic outcomes over 12 weeks in participants aged ≥50 years with

clinically defined knee OA, pain on most days, and VAS pain intensity ≥ 40 mm (n=133). Topical treatment using 4Jointz reduced pain compared to placebo (VAS -9.9 mm, $p=0.034$; KOOS pain scale +5.7, $p=0.047$), but had no effect on inflammation or cartilage breakdown over 12 weeks of treatment.

In the fourth study, efficacy of zoledronic acid (ZA: 5mg/100ml) vs placebo over 12 months in participants aged ≥ 50 years with clinically defined knee OA, pain on most days, VAS pain intensity ≥ 40 mm and a bone marrow lesion visible on T2-weighted MR images (n=59) was assessed. Treatment with ZA (compared to placebo) improved VAS pain scores after six months (-14.5 mm, $p=0.04$) but not after three or twelve months. ZA treatment reduced total BML area compared to placebo after six months (-175.7 mm^2 , $p=0.024$); with a trend after twelve months (-146.5 mm^2 , $p=0.095$). This provided the first evidence of a treatment to modify structural progression in OA.

In conclusion, this series of studies indicate that pain is a strong and stable musculoskeletal correlate of quality of life over time, vitamin D is a determinant of musculoskeletal pain, and treatment with 4Jointz and ZA are both effective in reducing pain. Additionally, ZA modifies structural progression by reducing total BML area; therefore, a lesion-specific approach to treatment of osteoarthritis pain is feasible. Future work should include targeting cognitive correlates of pain, clinical trials of vitamin D supplementation, and clinical trials of ZA to investigate effects on cartilage.

Personal acknowledgements

I thank my primary supervisor, Professor Graeme Jones. When I first met him at a conference in 2003, he recommended that if I wanted to continue a career in science I should complete a PhD, and that he would be happy to supervise me. In late 2008 I contacted him to discuss taking him up on his offer... and so the PhD journey began. His advice has continued to be equally sound and timely, and I consider him an outstanding mentor. He has given generously of his time, advice, wisdom, opportunities and financial assistance. His input into critical thinking, particularly the craft of writing papers has increased my skills as a researcher. I am extremely fortunate to have had him as my primary supervisor during my PhD and I thank him for the many contributions he has made.

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Dr Steve Quinn has been my statistical supervisor. Early on in my candidature, he was willing to sit with me while I ran new analyses to help me identify and solve problems, and I thank him for his patience and time in this early period. Steve is extremely talented as a theoretical and practical statistician, and I am indebted to him for new ways of thinking about the art of statistical analysis. I thank him for continuing to make time for me, especially when he moved from Hobart to Adelaide.

In this thesis, I have used data from the TASOAC study, the 4Jointz trial, and the ZAP trial. I thank the 1099 participants in the TASOAC study, the 59 participants in the ZAP trial and the 133 participants of the 4Jointz trial, who participated in these studies and without whom there would be no data.

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Laura Laslett
June 2013

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TASOAC

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4Jointz trial

I acknowledge Arthritis Relief Plus Ltd (Queensland, Australia), who provided tubes of 4Jointz and placebo, and finance for the study.

ZAP trial

I acknowledge Novartis Pharmaceuticals Australia for their funding of the ZAP trial and provision of zoledronic acid and placebo, and part-funding of the trial, and Prof Graeme Jones for his part-funding of the trial.

List of publications

Publications arising from this thesis:

Laslett LL, Quinn SJ, Winzenberg TM, Sanderson K, Cicuttini F, Jones G. A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. *BMC Musculoskelet Disord*. 2012;13(1):168.

Laslett LL, Dore DA, Quinn SJ, Winzenberg TM, Boon P, Jones G. Zoledronic acid reduces knee pain and bone marrow lesions over one year: a randomised controlled trial. *Ann Rheum Dis* 2012;71(8):1322-8.

Laslett LL, Quinn SJ, Darian-Smith E, Kwok M, Fedorova T, Körner H, Steels E, March L, Jones G. Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial. *Osteoarthritis Cartilage*. 2012, 20(11):1209-16.

Laslett LL, Quinn SJ, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a five year longitudinal study. Accepted for publication in *Ann Rheum Dis* in January 2013.

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Redmond CL, Bain GI, Laslett LL, McNeil JD. Hand syndromes associated with diabetes: impairments and obesity predict disability. *J Rheumatol*. 2009; 36:2766-71.

Wei S, Winzenberg T, Laslett LL, Venn A, Jones G. Oral contraceptive use and bone. *Curr Osteoporos Rep*, 2011;9(1):6-11.

Laslett LL, Lynch J, Sullivan TR, McNeil JD. Osteoporosis education improves osteoporosis knowledge and dietary calcium: comparison of a four week and a one-session education course. *Int J Rheum Dis*. 2011;14(3):239-47.

Valdes AM, De Wilde G, Doherty SA, Lories RJ, Vaughn FL, Laslett LL, Maciewicz RA, Soni A, Hart DJ, Zhang W, Muir KR, Dennison EM, Wheeler M, Leaverton P, Cooper C, Spector TD, Cicuttini F, Chapman V, Jones G, Arden NK, Doherty M. The Ile585Val TRPV1 variant is involved in risk of painful knee osteoarthritis. *Ann Rheum Dis*. 2011;70(9):1556-61.

Wei S, Venn A, Ding C, Foley S, Laslett L, Jones G. The association between oral contraceptive use, bone mineral density and fractures in women aged 50-80 years. *Contraception*. 2011 Oct;84(4):357-62.

Laslett LL, Just (nee Foley) SJ, Quinn SJ, Winzenberg TM, Jones G. Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study. *Osteoporos Int*. 2012;23(1): 67-74.

Redmond CL, Bain GI, Laslett LL, McNeil JD. Deteriorating tactile sensation in patients with hand syndromes associated with diabetes: a two-year observational study. *J Diabetes Complications* 2012;26(4):313-8.

Crisp A, Dixon T, Jones G, Cumming RG, Laslett LL, Bhatia K, Webster A, Ebeling PR. Declining incidence of osteoporotic hip fracture in Australia. *Arch Osteoporos*. 2012 DOI 10.1007/s11657-012-0095-y

Vos T, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163-96.

Murray CJ, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197-223.

Laslett LL, Kingsbury SR, Hensor EMA, Bowes MA, Conaghan PG. Effect of bisphosphonate use in patients with symptomatic and radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *Ann Rheum Dis*. 2013[epub before print].

Scientific presentations arising from the thesis

International conferences

- 2010 American Society for Bone and Mineral Research (Ontario, Canada).
Laslett LL, Just S, Quinn S, Winzenberg TM, Jones G. Measures of body fat are associated with prevalent vertebral deformities in older women (Poster presentation).
- 2011 European League Against Rheumatism (London, UK).
Laslett LL, Dore DA, Quinn SJ, Winzenberg TM, Boon P, Jones G. Zoledronic acid reduces bone marrow lesions and knee pain over one year (Oral presentation).
This abstract won the award for “Best abstract” in the osteoarthritis section (€1000). This very prestigious award placed our abstract in the top 12 out of 3000 abstracts and recognises the novelty of the research question and quality of our research.
- 2011 Osteoarthritis Research Society International Imaging conference (Salzburg, Austria).
Laslett LL, Dore DA, Quinn SJ, Winzenberg TM, Boon P, Jones G: Zoledronic acid reduces bone marrow lesions and knee pain over one year (Oral presentation).
I was awarded a Young Investigator Award (€700) for this abstract. I was one of the top 4 Young Investigators selected to give an oral presentation in this specialist conference.
I was also awarded half my travel costs (AUD\$1900) from the University of Tasmania’s Graduate Research Conference Support Fund in order to attend this conference.
- 2011 Australia and New Zealand Bone and Mineral Society and the International Osteoporosis Foundation Regionals (Gold Coast, Australia).
Laslett LL, Quinn SJ, Winzenberg TM, Jones G, Ding C. Low vitamin D predicts change in knee and hip pain over five years (Oral presentation).
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I received a travel bursary to attend this conference and present this work (AUD\$350).
- 2011 American College of Rheumatology (Chicago, USA).
Hall J, Laslett LL, Martel-Pelletier J, Pelletier J-P, Abram F, Ding C, Cicuttini F and Jones G. Change in knee cartilage volume and incident meniscal extrusion as predictors of change in joint space width of the tibiofemoral joint: 5 year longitudinal study (Oral presentation).
(Note: J Hall and LL Laslett joint first authors)
This is a prestigious honour as only 5% of submitted abstracts are awarded an oral presentation.
- 2012 European Congress on Osteoarthritis and Osteoporosis (Bordeaux, France)

Laslett LL, Quinn SJ, Darian-Smith E, Kwok M, Fedorova T, Körner H, Steels E, March L, Jones G. Treatment with 4jointz reduces knee pain over twelve weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial (Poster presentation).

National conferences

- 2010 Australian Rheumatology Association (Melbourne).
Laslett LL, Winzenberg TM, Quinn S, Jones G. Musculoskeletal determinants of quality of life in a community dwelling cohort of older people (Poster presentation).
This poster won the award for “Best Clinical Poster” (AUD\$500).
- 2010 Australia and New Zealand Bone and Mineral Society (Adelaide).
Laslett LL, Just (nee Foley) SJ, Quinn SJ, Winzenberg TM, Jones G. Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study (Poster presentation).
- 2012 Australian Rheumatology Association (Canberra).
Laslett LL, Quinn SJ, Darian-Smith E, Kwok M, Fedorova T, March L, Jones G. Treatment with 4jointz reduces knee pain over twelve weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial (Poster presentation).
- 2012 Population Health Congress (Adelaide, Australia).
Laslett LL, Quinn SJ, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. Serum vitamin D and change in knee and hip pain in older adults over five years (Oral presentation).
I received a travel bursary to attend this conference and present this work (AUD\$450).

Local conferences

- 2010 Sharing Excellence in Research, Graduate Research Conference of the University of Tasmania (Hobart).
Laslett LL, Quinn SJ, Winzenberg TM, Jones G. Musculoskeletal determinants of quality of life in a community dwelling cohort of older people (Oral presentation).
- 2011 Sharing Excellence in Research, Graduate Research Conference of the University of Tasmania (Hobart).
Laslett LL, Dore DA, Quinn SJ, Winzenberg TM, Boon P, Jones G: Zoledronic acid reduces bone marrow lesions and knee pain over one year (Poster presentation).
This abstract won the award for “Best poster and best poster defence” (AUD\$1000), as it was the top ranked poster of all posters presented at the University of Tasmania’s yearly postgraduate research conference.
- 2012 Sharing Excellence in Research conference (UTas postgraduate conference, Hobart).
Laslett LL, Quinn SJ, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. Moderate vitamin D deficiency is associated with

new or worsening knee and hip pain in older adults: a five year longitudinal study (Poster presentation).

Awards resulting from thesis material

- 2010 Poster Prize: Best Clinical Poster at the Australian Rheumatology Association conference (Melbourne) for the poster “Musculoskeletal determinants of quality of life in a community dwelling cohort of older people”.
- 2010 Travel grant to attend the Australia and New Zealand Bone and Mineral Society (ANZBMS) Annual Scientific Meeting in Adelaide to present the poster entitled “Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study”.
- 2011 Abstract Prize: Best abstract, Osteoarthritis section, European League against Rheumatism (EULAR) conference, London. Abstract title “Zoledronic acid reduces bone marrow lesions and knee pain over one year.”
- 2011 Poster prize: Best poster and best poster defence at the Sharing Excellence in Research Conference (UTas Graduate Research), Hobart for the poster entitled “Zoledronic acid reduces bone marrow lesions and knee pain over one year”.
- 2011 Travel grant to attend the Australia and New Zealand Bone and Mineral Society (ANZBMS) and the International Osteoporosis Foundation Regionals (Gold Coast). Annual Scientific Meeting in the Gold Coast. I gave an oral presentation entitled “Low vitamin D predicts change in knee and hip pain over five years” and defended a poster entitled “Zoledronic acid reduces bone marrow lesions and knee pain over one year”.
- 2012 Bursary to attend the Population Health Congress in Adelaide, Australia. I gave an oral presentation entitled “Serum vitamin D and change in knee and hip pain in older adults over five years”.

Other items awarded during candidature

- 2012 Arthritis Australia Fellowship 2013 (AUD\$50,000). This is a competitive award offered to a junior investigator to further work in osteoarthritis. Only one fellowship is awarded annually.
- 2012 OARSI Young Investigator Scholarship (US\$6500), March 2012. This is a competitive and prestigious award from the Osteoarthritis Research Society International (OARSI) which enabled travel to the UK for a 3 month placement at the Division of Rheumatic and Musculoskeletal Disease and NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds. Only 5 were awarded internationally.
- 2012 Menzies Research Institute Tasmania Postgraduate Student Prize, for best postgraduate student, awarded on the basis of excellent research achievement over the preceding 12 months (AUD\$2000).

List of abbreviations and approximate meanings

25–OHD	25-hydroxyvitamin D: the activated form of the hormone Vitamin D
ACR	American College of Rheumatology
AQoL	Assessment of Quality of Life: a questionnaire for assessing the quality of a person's life
BMI	Body mass index: Quetelet's index, a measure of fatness
BMD	Bone mineral density: a two dimensional measure of bone density
BML	Bone marrow lesion: a hypointense region in the bone marrow, as visualised by magnetic resonance imaging
COX–2	cyclooxygenase–2: an enzyme responsible for inflammation and pain
CTX–2	C-terminal cross linking telopeptide of type II collagen: a marker of cartilage tissue degradation
DXA	Dual energy X-ray absorptiometry: the current gold standard for measuring bone mineral density
eGFR	estimated glomerular filtration rate: a measure of kidney function.
FFQ	Food frequency questionnaire: a dietary questionnaire
fMRI	functional magnetic resonance imaging: an MRI procedure that measures brain activity by detecting associated changes in blood flow
ICC	Intraclass correlation coefficient: a measure of the consistency of measurements made by multiple observers measuring the same data
IL–6	Interleukin–6, a marker of inflammation
IRR	Incident rate ratio: a measure of relative risk
JSN	Joint space narrowing: narrowing of the space between tibia and femur, as seen on standing radiographs, inferring loss of cartilage
JSW	Joint space width: the space between tibia and femur, as seen on standing radiographs
KOOS	Knee Injury and Osteoarthritis Outcome Score: a questionnaire measure of knee pain and function

MR	Magnetic resonance
MRI	Magnetic resonance imaging: a family of imaging techniques enabling detailed visualisation of internal structures
NSAID	Non-steroidal anti-inflammatory drugs: nonselective inhibitors of both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes, thereby reducing pain and inflammation. Examples include aspirin, ibuprofen, naproxen and cyclooxygenase-2 inhibitors such as celecoxib
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OARSI-OMERACT responder criteria	Osteoarthritis Research Society International (OARSI) standing committee for clinical trials response criteria initiative and the outcome measures in rheumatology (OMERACT) committee, which in conjunction with the rheumatology community has led to the development of a uniform core set of outcome measures for osteoarthritis
OMERACT	Outcome measures in rheumatology committee
OR	Odds ratio: a measure of effect size
P1	Baseline (Phase 1) of TASOAC, the Tasmanian older adult cohort study
P2	The 2.6 year follow up (Phase 2) of the TASOAC study
P3	The 5 year follow up (Phase 3) of the TASOAC study
QALY	Quality adjusted life year: a metric used in health economics to adjust years of life for the quality of the person's life.
QoL	Quality of life
RCT	Randomised controlled trial
ROA	Radiographic osteoarthritis: aspects of osteoarthritis as seen on radiographs
SD	Standard deviation: a measure of variation within a data set
SE	Standard error: a measure of variation within a data set
TASOAC	The Tasmanian Older Adult Cohort Study
VAS	Visual analog score: a tool for measuring pain intensity

WOMAC Western Ontario and McMaster Universities Index of
Osteoarthritis: a measure of knee and hip functioning

Note: Abbreviations appearing only in summary tables of treatment modalities are not shown here.

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Chapter 1: Introduction to the determinants, correlates and modifiers of musculoskeletal pain

Chapter 1. Introduction to the determinants, correlates and modifiers of musculoskeletal pain

1.1 The importance and prevalence of pain

Pain, the “unpleasant sensation associated with actual or potential tissue damage...” (Dirckx, 1997), is a familiar human experience. It is an important clinical symptom, and a priority for patients (Heiberg and Kvien, 2002).

Musculoskeletal pain predicts numerous clinically relevant outcomes, including service use (Dominick, 2004), disability (Croft, 2005) and joint replacements (Gossec, 2005; Hawker, 2006; Conaghan, 2010; Jüni, 2003).

Two important characteristics of pain are its frequency and intensity. The exact prevalence of pain in any particular group depends upon the definition used (Pereira, 2011) and the time reference. Overall prevalence of musculoskeletal pain in community-dwelling adults appears to be approximately 45–66% (Picavet and Schouten, 2003; Thomas, 2004; Zhai, 2006), and the prevalence of pain at most sites increases with advancing age (Picavet and Schouten, 2003; Urwin, 1998), and is higher in women (Picavet and Schouten, 2003; Zhai, 2006; Keenan, 2006).

Knees are either the most common (Keenan, 2006; Thomas, 2004) or one of the most common sites of joint pain in older people (Picavet and Schouten, 2003). Pain of the hip or knee are also the sites in which the greatest age-related increases in prevalence occurred (Picavet and Schouten, 2003).

Joint pain typically affects multiple joints (Picavet and Schouten, 2003; Keenan, 2006; Thomas, 2004; Dawson, 2004).

1.2 Arthritis

The most common cause of chronic pain in older people is arthritis (Peat, 2001; Britt, 2010), from the Greek *arthron* (joint) and *-itis* meaning (inflammation)), thereby being a (painful) disease characterised by inflammation of a joint or joints (Dirckx, 1997)

1.2.1 Disease burden and economic impact

Based on self-reports, estimates from the 2007–08 National Health Survey found that more than 6.3 million Australians (31%) have arthritis or some other musculoskeletal condition. The most common type of arthritis is osteoarthritis (OA), affecting 1.6 million Australians (8% of the population), followed by rheumatoid arthritis, which is estimated to affect 429,000 Australians (2%). (Australia's Health 2010 (AIHW, 2010)). OA predominantly affects the large joints.

Of the 561,300 respondents to the National Health Survey who listed arthritis or a related disorder as their main health condition, 30% rated limitations in their core activities as severe or profound (ABS, 2003), showing that arthritis can be extremely disabling. Arthritis and musculoskeletal conditions constituted the fourth largest component of direct health expenditure in 2004–05, at 7.5% of allocated health expenditure or AUD\$4.0 billion (AIHW, 2009), after cardiovascular diseases (\$5.9 billion), oral health (\$5.3 billion) and mental disorders (\$4.1 billion). Osteoarthritis costs are dominated by admitted patient services, mostly related to knee and hip joint replacements (AIHW, 2009), whereas in persons with rheumatoid arthritis, around half of the direct costs were for prescription pharmaceuticals. Actual expenditure on arthritis and musculoskeletal conditions increased from the 2000–01 to 2004–05 estimates, increasing annually by around 5.2% (after adjusting for inflation and excluding research expenditure). Increases in

expenditure are predicted to continue by an estimated 223% between 2002–03 and 2032–33 (Goss, 2008). Ageing, increases in the volume of treatment(s) per case, and growing population are cited as the factors driving these cost increases. Therefore, arthritis is common, disabling and expensive. The burden of musculoskeletal disorders on the community has been recognised on both national and international levels, with the Australian Government declaring arthritis and musculoskeletal conditions as a national health priority area in 2002, and at an international level with 2000–2010 declared the Bone and Joint Decade.

1.2.2 General definitions of osteoarthritis

OA was once described as a degenerative, or “wear and tear” disease, but this is now considered incorrect (Creamer and Hochberg, 1997; Loeser, 2012). Osteoarthritis is now defined as a “progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues.... this ultimately results in the breakdown of cartilage and bone, leading to symptoms of pain, stiffness and functional disability” (Lane, 2011).

Therefore, osteoarthritis is a disease of the whole joint, and although its signature pathologic features are articular cartilage loss and damage of adjacent bone (Arden and Nevitt, 2006), it commonly involves many other joint structures including subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves, and synovium (Lane, 2011; Loeser, 2012). The failure of these joint tissues results in a common outcome – pain and reduced function (Creamer and Hochberg, 1997), but involve no common pathological pathway (Lane, 2011). Therefore, there must be a range of determinants of

disease, with different entities as potential therapeutic targets, not all of which will benefit the entire patient population with osteoarthritis.

1.3 The nexus of pain and osteoarthritis: Radiographic vs. clinical definitions of osteoarthritis

Osteoarthritis has historically been defined in two ways: firstly, using features visible on radiographs without reference to pain. Examples include the classic grading system of Kellgren and Lawrence (Kellgren and Lawrence, 1957) (see Table 1.1), or the more recent OARSI grading system (Altman, 1995), for grading osteoarthritis according to individual features visible on radiographs (from 0–3, where 0=absent and 3=severe), rather than the joint as a whole. Some advantages of using these radiographic classifications are that they are objective, can be standardised, and the technology is well-established, but disadvantages include the lack of correlation to the most important concern of patients (pain) (Heiberg and Kvien, 2002), the inability to visualise non-calcified tissues, their two-dimensional nature, measurement error and semi-quantitative assessment (Jones, 2004).

Table 1.1. Radiographic criteria for assessment of osteoarthritis using the Kellgren and Lawrence (KL) grading system

Definition grades	Description
Grade 0: No osteoarthritis	No features of osteoarthritis
Grade 1: Doubtful	Minute osteophyte, doubtful significance
Grade 2: Mild	Definite osteophytes, unimpaired joint space
Grade 3: Moderate	Moderate diminution of joint space
Grade 4: Severe	Joint space greatly impaired with sclerosis of subchondral bone

From Arden and Nevitt, 2006; based on Kellgren and Lawrence, 1957.

Secondly, OA can be defined clinically, such as the American College of Rheumatology (ACR) definition which does include pain, specifically “pain for most days of the month”, in addition to other clinical features (Altman, 1986).

These definitions are most useful for epidemiological and clinical studies

rather than clinical practice, as the initial criteria were designed to differentiate patients with OA from those with rheumatoid arthritis (McAlindon and Dieppe, 1989).

The relative importance of pain versus radiographic or imaging findings in osteoarthritis is the subject of some debate (Cibere, 2006; LaValley, 2001). Radiologic features are poor predictors of clinical outcomes, certainly in knee osteoarthritis (Bruyere, 2002). Radiographic markers of osteoarthritis are only weakly associated with pain (Bedson and Croft, 2008; Hannan, 2000; Michel, 1997; Dahaghin, 2005), with only 15–53% of persons with knee pain having prevalent radiographic OA using a global assessment scale, such as the Kellgren–Lawrence system (Cibere, 2006). Results of a systematic review and literature search investigating putative discordance between clinical and radiographic knee osteoarthritis (Bedson and Croft, 2008) concluded that reported discordance exists due to the nature and extent of radiographic views (for example, patellofemoral joint views are often omitted), how symptoms are defined, and the nature of the study group (Bedson and Croft, 2008). When authors have attempted to control for potential reasons for discordance, observed discordance reduces (Duncan, 2007). However, lack of concordance does not equate to lack of aetiologic association. This apparent discordance may simply reflect that there are many other factors that cause pain other than structures that appear on radiographs.

Newer imaging modalities such as MRI allow visualisation of other structures which have been associated with pain (Felson, 2001; Speer, 1992; Koo, 1999; Zhang, 2011), and a study from our centre showed that radiographic features of knee OA (osteophytes, knee JSN) were not associated with prevalent knee pain after adjustment for other structural factors (Zhai, 2006).

Therefore, it is clear that that investigation into correlates, determinants and modifiers of musculoskeletal pain must look beyond radiographs.

1.4 Pain

1.4.1 Correlates of pain

Numerous studies have investigated correlates of pain, including demographic and social factors as well as associations between features of OA visible on radiographs and MR imaging. Correlates at several sites are discussed in detail as follows.

1.4.1.1 Knee

Non-psychological correlates of knee pain have been well reviewed in Jones et al, 2011 (Jones, 2011). Obesity, weak muscles, and numerous structures have been independently associated with pain. These structures include bone marrow lesions, cartilage defects, meniscal tears (posterior horn), osteophytes (but not independently of MRI changes), joint effusions, and synovitis. Tibial bone size, subchondral bone mass, meniscal extrusion and cartilage volume are not associated with pain, and associations between anterior cruciate ligament tears and knee pain are controversial (Jones, 2011). In our cohort, both prevalent knee pain and more severe knee pain is associated with: increasing body mass index (BMI), reduced knee extension strength, bone marrow lesions (BMLs), full-thickness and non-full-thickness chondral defects of the medial tibial compartment, and hip (but not knee) joint space narrowing (JSN), but not osteophytes (Zhai, 2006).

1.4.1.2 Hip

Less attention has been directed to pain at other sites. With regards to pain in the hip, only a few authors investigated multiple correlates of hip pain (Hopman-Rock, 1996; Juhakoski, 2008; Summers, 1988; Thumboo, 2002; van Baar, 1998), with only one of these studies solely investigating

persons with hip pain (Juhakoski, 2008) rather than a mixed population of people with knee and hip pain.

Associations have been observed between number of comorbidities, duration of concomitant knee pain, and life satisfaction, but not BMI, radiologic score of hip OA, leg extensor strength or depression (as measured by the Beck Depression Inventory (Juhakoski, 2008). BMI was associated with WOMAC function scores, but not WOMAC pain (Juhakoski, 2008).

Regarding radiographic features of hip OA, synovitis, and possibly labrum hip BMLs have been associated with hip pain cross-sectionally, after adjustment for age, sex and BMI (Roemer, 2011). In another cross-sectional study, BML size was found to be related to the magnitude of hip pain (Taljanovic, 2008). Indeed, prevalence of BMLs and synovitis was 100% in a sample of patients with severe hip pain and rapidly progressing radiologic features of hip OA (Boutry, 2002).

1.4.1.3 Low back

Cross-sectional correlates of low back pain include previous back injury, physical and mental stress at work (Heliovaara, 1991), social deprivation (Croft and Rigby, 1994; Webb, 2003) and pain at other sites (Heliovaara, 1991; Webb, 2003). Correlations between low back pain and clinical findings on physical examination are poor (Michel, 1997). A systematic review of cohort studies found that psychological factors (notably distress, depressive mood, and somatization) are implicated in the transition from acute to chronic low back pain (Pincus, 2002). Conflicting findings on the association between obesity and smoking with low back pain are discussed later (see section 1.4.1.5: “Correlates across sites” on page 43).

Presence of vertebral endplate signal changes visible on MR imaging (Modic changes) (de Roos, 1987; Modic, 1988) have been consistently associated with low back pain symptoms, with a systematic review reporting significant associations between Modic changes and low back pain (OR's from 2.0 to 19.9) (Jensen, 2008). Patients with persistent Type 1 Modic changes have poor prognosis over a follow up period of 14 months (Jensen, 2012), but unlike knee BMLs, there is no association between the change in size of type 1 Modic changes and change in low back pain intensity (OR 1.0) (Jensen, 2012).

1.4.1.4 Hand

Dahaghin and colleagues (Dahaghin, 2005) investigated correlates of hand pain, finding that pain in the neck and shoulder, OA of any joint, female sex, and presence of rheumatoid arthritis or a thyroid disorder were all associated with hand pain in a multivariate model; but that diabetes, obesity, previous fracture of the wrist or hand, or having a manual occupation were not. The evidence for an association between radiographic OA and hand function impairment is inconsistent, ranging from no association to a moderate association (Dahaghin, 2006). Assessment of features using ultrasound imaging, which showed that while persons with painful joints are more likely to demonstrate ultrasound-detected pathology, the extent or total amount of pathology observed did not correlate with symptoms (Keen, 2008), but the sample size was small. Using MR imaging, synovitis, BMLs, erosions and attrition have been associated with joint tenderness (Haugen, 2012). Therefore, if pathological features are associated with pain, it appears more likely that it will be the features visible on ultrasound and MR imaging rather than those visible only on radiographs which are associated with pain.

1.4.1.5 Correlates across sites

Consistent correlates of pain across sites include psychological factors, poor muscle strength, some OA features visible on MR imaging (eg BMLs, synovitis), and pain in other joints. Features visible only on radiographs (eg joint space narrowing) are consistently shown to be poorly correlated with pain. Psychological factors are discussed in more detail in section 1.4.3 (page 47). Overall, many studies only investigate a few factors in cross-sectional studies, whereas longitudinal studies are required to assess changes over time.

BMI has been consistently associated with knee pain (Zhai, 2006; Felson, 2000) and low back pain (Leboeuf-Yde, 2000), but the lack of association in the only study of multiple correlates of hip pain (Juhakoski, 2008) suggests that at least some correlates of pain may differ by site of pain, a theory supported by other authors (Adamson, 2006; Janke, 2007). Adamson (2006) (65) (65) (65) reported cross-sectional associations between obesity and pain in the lower limbs but not in the upper limbs, after adjustment for sex, cigarette smoking, alcohol consumption and socio-economic class. A review of 65 studies investigating obesity and low back pain found that while obesity was weakly associated with low back pain, results were inconsistent (Leboeuf-Yde, 2000). However, these studies have used weight, BMI and waist-hip ratio, which do not provide information about specific components of body composition and therefore no clues as to possible mechanisms of action. A recent cross-sectional study investigated the effect of different aspects of excess weight which may explain these discrepancies. In multivariate analysis, they found that BMI was associated with low back pain, as was total fat mass and lower limb fat mass (and possibly upper limb fat mass), independent of lean mass, but that lean mass

was not associated with pain independent of fat mass (Urquhart, 2011). This suggests that the relationship between obesity and low back pain intensity includes spinal loading as well as metabolic factors.

Adamson (2006) (65) (65) (65) also reported associations between cigarette smoking and pain in the upper limbs after adjustment for sex, alcohol consumption and socio-economic class. This reached statistical significance for back and shoulder pain, but not at other sites (Adamson, 2006). There has been significant debate about the role of cigarette smoking as a correlate or cause of pain and OA, particularly in the light of a recent study (a longitudinal observational study following up a cohort who had taken part in an earlier randomised controlled trial). This demonstrated a strong inverse dose-response relationship between duration of smoking and risk of lower limb total joint replacement (Mnatzaganian, 2011). This is in contrast to data from other observational studies, which show that the protective effect of smoking in OA is likely to be false and related to selection bias in the control populations of case-control studies, as it was observed only in hospital-based case-control studies (Hui, 2011; Gill and Hill, 2012). Indeed, our data suggest smoking is detrimental for spinal OA (Jones, 1998), and cartilage loss in the knee (Ding, 2008) in cross-sectional studies.

1.4.2 Pathogenesis of pain

The pathogenesis of pain is complex and multifactorial, involving local nociception, inflammatory mediators, and central sensitisation.

Normal cartilage is aneural, but abnormal cartilage is not, with evidence of substance P nociceptive fibres in osteoarthritic cartilage (Fortier and Nixon, 1997; Wojtys, 1990), suggesting that these fibres are involved in the signalling and maintenance of pain associated with OA. Other work has demonstrated that prostaglandins are differently regulated in normal and OA-affected chondrocytes, with up-regulation of cyclooxygenase-2 (COX-2) in cartilage specimens from persons with OA, leading to a 50 fold increase in prostaglandin E₂ (Amin, 1997), which then stimulates bone resorption (Robinson, 1975). This all suggests that abnormal cartilage has a direct role as a source of pain. There is increasing interest in the subchondral bone in the pathogenesis of OA, and therefore it is interesting and relevant that substance P nociceptive fibres have also been found in the subchondral bone (Wojtys, 1990).

Inflammatory processes are implicated in the pathogenesis of musculoskeletal pain. Inflammation can be localised (eg synovitis) or systemic, as indicated by changes in inflammatory markers such as IL-6. Biopsies of patients with both early and late knee OA have shown low-grade chronic synovitis with production of pro-inflammatory cytokines (Smith, 2003; Benito, 2005). Synovitis has been associated with fluctuations in pain (Hill, 2007; Zhang, 2011), and interventions aimed at the synovium are effective in treating knee pain, such as intra-articular injections of local anaesthetic (Creamer, 1996), and corticosteroids

(Dieppe, 1980; Ostergaard, 1996; Raynauld, 2003). Since other evidence suggests that the synovium is richly innervated (Kidd, 1996), overall, this data suggests that there is an intra-articular component to knee pain, and that this is likely to be due to inflammatory factors.

The consistent association between presence of BMLs and knee pain (Felson, 2001; Felson, 2007; Zhang, 2011; Zhai, 2006), and Carbone's observations that BMLs were significantly less common in users of alendronate and oestrogen (Carbone, 2004) suggest that bisphosphonates and BMLs (and indeed the subchondral bone as a whole) may provide insights in the pathogenesis of pain as well as potential treatments (see Chapter 1.5.3 for further exploration of this second theme). BML-related pain could be osteoclast-mediated, since this is one mechanism of action of nitrogen-containing bisphosphonates (Rogers, 2003), and a known mechanism of bone pain in cancer (Honore and Mantyh, 2000), which is often treated with bisphosphonates.

Bisphosphonates may work through a variety of mechanisms, including effects on the subchondral bone and osteochondral junction. Abnormal bone turnover in OA leads to a zone of osteoporosis beneath the thickened subchondral plate, altered flexibility, and increased microfracture (Buckland-Wright, 2007). Osteoclasts mediate the extension of channels from marrow spaces into the non-calcified articular cartilage. The resulting loss of osteochondral integrity exposes subchondral nerves to pro-inflammatory and algescic factors from the synovial fluid and permits sensory nerve growth into the non-calcified articular cartilage (Walsh, 2010). Furthermore, osteoclasts may reduce pH at the osteochondral junction, thereby sensitizing and activating sensory nerves through actions on ion channels on their peripheral

terminals (Yoneda, 2011). Bisphosphonates are also reported to have anti-inflammatory actions (Roelofs, 2010; Baroja-Mazo and Pelegrin, 2012); such effects may play a role in an immediate analgesic benefit, as distinct from that which might arise as a consequence of osteochondral structural alteration. Overall, it is clear that the pathogenesis of joint pain is complex and multifactorial, involving local nociception, inflammatory mediators, and central sensitisation (Dieppe and Lohmander, 2005; Kidd, 1996; Schaible and Grubb, 1993), but also that a lesion-specific approach is feasible in treating joint pain.

1.4.3 Other determinants of pain

The pain experienced by an individual is strongly influenced by genetics (Foulkes and Wood, 2008), including genes for thermal pain sensitivity. For example, analyses completed by UK colleagues in collaboration with our group used pooled data from 7 cohorts (including TASOAC) demonstrated that persons having the *TRPV1* 585 Ile–Ile genotype (associated with lowered peripheral pain sensitivity) were at decreased risk of knee OA being painful (OR 0.74) (Valdes, 2011). This further demonstrates that factors other than radiographic changes influence pain.

Vitamin D has also been implicated in the pathogenesis of knee pain, as vitamin D deficiency is common in persons with widespread bone and muscle pain (McBeth, 2010; Plotnikoff and Quigley, 2003; Block, 2004; Al Faraj and Al Mutairi, 2003; Nellen, 1996; Serhan, 1999), although this could be reverse causality through the effects of ill health on sunlight exposure and physical activity. The active metabolite 1,25(OH)₂D has an antiproliferative effect and down-regulates inflammatory markers (Lips, 2006). We have demonstrated

in a smaller sample of our cohort that inflammatory markers are associated with change in non-weight bearing knee pain (Stannus, 2013). Other authors have shown that low levels of 25–OHD predicted increased experimental pain sensitivity (Glover, 2012), suggesting that vitamin D level may be related to pain pathways involved in initial perception of pain.

Cognitive, psychological, and psychosocial aspects also influence pain (Keefe and Somers, 2010; Creamer, 1999), with depressed persons experiencing more rapid worsening in knee pain than non–depressed persons (Riddle, 2011). Causality also occurs in the opposite direction; osteoarthritic knee or hip pain were determinants of subsequent depressed mood through its effect on fatigue and disability (Hawker, 2011).

Pain catastrophisation has been extensively investigated. It refers to the tendency to focus on and magnify pain sensations, and to feel helpless in the face of pain (Sullivan, 2001). It explains a higher proportion of variance in pain cross–sectionally than demographic and medical status variables combined (Somers, 2009) and mediates the gender–pain relationship even after controlling for depression (Keefe, 2000). Catastrophisation is related to pain severity, pain–related disability, poor outcomes of pain treatment, and possibly inflammatory disease activity (Edwards, 2006).

1.5 Treatment options for modifying musculoskeletal pain

There are a number of treatment options for modifying musculoskeletal pain.

Guidelines for the use of these therapies for OA of the knee and hip have been developed by the relevant professional society (OARSI) (Zhang, 2008). Optimal management of the symptoms of hip and knee OA include a combination of non-pharmacological and pharmacological modalities (Zhang, 2008), with provision of information about the disease process and lifestyle modification, physical activity, weight loss and appropriate referral to health professionals eg physiotherapist. The initial oral analgesic for pain relief is paracetamol (<4g/day) followed by non-steroidal anti-inflammatory drugs, COX-2 selective agents or non-selective NSAIDs co-prescribed with proton-pump inhibitors for prevention of gastro-intestinal side effects. If pain persists, other available therapies include capsaicin, injections of corticosteroids, glucosamine sulphate, chondroitin sulphate, and weak opioids. Patients who continue to have inadequate pain relief and functional improvement may consider joint replacement surgery (Zhang, 2008).

1.5.1 Evidence for efficacy of pain treatments

Evidence summaries have now been developed for treatment of musculoskeletal pain, within the context of knee and hip OA (Zhang, 2010). Table 1.2 has been reprinted from Osteoarthritis Cartilage, Vol 18, Zhang W *et al.* OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009, pg 476-99, Copyright (2010), with permission from Elsevier. Effect sizes (ES) are standard mean difference (i.e., the mean difference between a treatment and a control group

divided by the standard deviation of the difference), and are presented for function and stiffness. References to original papers have been omitted.

Table 1.2: Best evidence for treatment efficacy for pain outcomes, from various modalities of therapy for hip and knee OA available 31 January 2009 (from Zhang, 2010)

Modality	Joint	QoS (%)	LoE	Effect size for pain (95% CI)	NNT (95% CI)
<i><u>Non-pharmacological</u></i>					
Self-management	Both	100	Ia	0.06 (0.02, 0.10)	
Telephone	Both	100	Ia	0.12 (0.00, 0.24)	
Education	Both	100	Ia	0.06 (0.03, 0.10)	
Strengthening	Knee	100	Ia	0.32 (0.23, 0.42)	
	Hip	100	Ia	0.38 (0.08, 0.68)	
Aerobic	Knee	100	Ia	0.52 (0.34, 0.70)	
Water-based exercise	Both	100	Ia	0.19 (0.04, 0.35)	
Balneotherapy	Knee	75	Ia		NS
Spa/sauna	Both	75	Ib	0.46 (0.17, 0.75)	NS
Weight reduction	Knee	100	Ia	0.20 (0.00, 0.39)	3 (2, 9)
TENS	Both	75	Ia		2 (1, 5)
Laser	Both	100	Ia		4 (2,17)
Ultrasound	Both	50	Ia	0.06 (-0.39, 0.52)	
Radiotherapy	Both	50	IIb	Similar effects between OA and RA from an MA of uncontrolled trial	
Heat/ice	Knee	75	Ia	0.69 (-0.07, 1.45)	
Massage	Knee	40	Ib	0.10 (-0.23, 0.43)	
Acupuncture	Knee	100	Ia	0.35 (0.15, 0.55)	4 (3, 9)
Insoles	Knee	100	Ia	No different between type of insoles, no placebo/usual care comparisons	
Joint protection (braces)	Knee	100	Ia	More benefits with a knee brace than a neoprene sleeve	
Electrotherapy/EMG	Knee	100	Ia	0.16 (-0.08, 0.39)	

(Table continues on the next page)

Table 1.2 Best evidence for treatment efficacy for pain outcomes (cont.)

Modality	Joint	QoS (%)	LoE	Effect size for pain (95% CI)	NNT (95% CI)
<i>Pharmacological</i>					
Acetaminophen	Both	100	Ia	0.14 (0.05, 0.23)	3 (2, 52)
NSAIDs	Both	100	Ia	0.29 (0.22, 0.35)	
Cox-2 inhibitors	Both	100	Ia	0.44 (0.33, 0.55)	
Topical NSAIDs	Knee	100	Ia	0.44 (0.27, 0.62)	
Topical capsaicin	Knee	75	Ia		4 (3, 5)
Opioids	Any	100	Ia	0.78 (0.59, 0.98)	
IA corticosteroid	Knee	100	Ia	0.58 (0.34, 0.75)	5 (3, 38)
IAHA	Knee	100	Ia	0.60 (0.37, 0.83)	7 (3, 119)
Glucosamine sulphate	Both	100	Ia	0.58 (0.30, 0.87)	5 (4, 7)
Glucosamine hydrochloride	Knee	–	Ib	-0.02 (-0.15, 0.11)	
Chondroitin sulphate	Knee	100	Ia	0.75 (0.50, 1.01)	5 (4, 7)
Diacerhein	Both	–	Ib	0.24 (0.08, 0.39)	
ASU	Both	100	Ia	0.38 (0.01, 0.76)	6 (4, 21)
Rosehip	Both	100	Ia	0.37 (0.13, 0.60)	6 (4, 13)
SAM-e	Knee	100	Ia	0.22 (-0.25, 0.69)	
<i>Surgical</i>					
Lavage/debridement	Knee	–	Ib	0.21 (-0.12, 0.54)	
Patellar resurfacing	Knee	100	Ib		9 (5, 25)
Osteotomy	Knee	100	Ia	Head to head comparisons, no placebo or conservative therapy controlled trials. HTO improves pain and Similar function improvement as TKR or HTO, but less complications and revision than HTO	
Unicompartment knee arthroplasty	Knee	75	SR cohort	Similar function improvement as TKR or HTO, but less complications and revision than HTO	
TJR	Both	100	III	TJR is effective to improve QoL, more beneficial for hip OA from an SR of cohort studies	

Abbreviations: ASU: avocado soybean unsaponifiables; EMG: electromyography; HTO: high tibial osteotomy; IA: intra-articular; IAHA: intra-articular hyaluronic acid; LoE: level of evidence; SAM-e: S-adenosylmethionine; SR: systematic review; TENS: trans cutaneous electrical nerve stimulation; TKR: total knee replacement; NNT: number needed to treat; NS: not significant; TJR: total joint replacement. Ia: Meta-analysis of RCTs; Ib: RCT; IIa controlled study without randomisation; IIb: quasi-experimental study (e.g., uncontrolled trial, one arm dose-response trial, etc.); III: observational studies (e.g., case-control, cohort, cross-sectional studies); IV: expert opinion.

QoS (highest quality of study) was assessed using validated scales, e.g., the Oxman and Guyatt scale for systematic review and the Jadad's scale for clinical trials. The percentage score was calculated for each study. The best available evidence was presented, i.e., SR with the highest quality, RCT with highest quality followed by uncontrolled or quasi experiment, cohort and case-control study. ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large; NNT for symptom relief, unless otherwise specified.

These treatments (with the possible exception of glucosamine sulphate and chondroitin) are not disease modifying. Therefore, they provide symptomatic relief, but do not change the disease process.

The most effective of the non-pharmacological therapies are exercise, thermal therapies (spa / heat / ice) and acupuncture. Paracetamol has a very small effect size (0.14), while NSAIDs and COX-2 inhibitors have small effect sizes (0.29 and 0.44). Opioids and corticosteroids have large effect sizes (0.78 and 0.75), but overall the effect sizes for pain are well below the level of pain relief desired by patients. Therefore, there remains considerable scope for additional therapeutic modalities for pain relief from musculoskeletal pain.

1.5.2 Evidence for side effects of pain treatments

Pharmacological therapies have benefits, but they also have side effects

associated with their use. These are summarised in Table 1.3, with

references in the original text (Zhang, 2010).

Table 1.3: Side effects associated with pharmacological therapies. Adapted from Zhang, 2010

Intervention	Adverse events	RR/OR (95% CI)	Evidence
Acetaminophen (paracetamol)	GI discomfort	0.80 (0.27, 2.37)	Meta-RCTs
	GI perforation/bleed	3.60 (2.60, 5.10)	CC
	GI bleeding	1.20 (0.80, 1.70)	Meta-CCs
	GI hospitalisation	1.20 (1.03, 1.40)	CS
	Renal failure	0.83 (0.50, 1.39)	CS
	Renal failure	2.50 (1.70, 3.60)	CC
NSAIDs	GI perforation/ulcer/bleed	5.36 (1.79, 16.10)	Meta-RCTs
	GI perforation/ulcer/bleed	2.70 (2.10, 3.50)	Meta-CSs
	GI perforation/ulcer/bleed	3.00 (2.50, 3.70)	Meta-CCs
	GI hospitalisation	1.63 (1.44, 1.85)	CS
	Myocardial infarction	1.09 (1.02, 1.15)	Meta-CSs
Topical NSAIDs	GI events	0.81 (0.43, 1.56)	Meta-RCTs
	GI bleed/perforation	1.45 (0.84, 2.50)	Case– control
	Serious GI complications	0.33 (0.01, 8.14)	Meta-RCTs
	Symptomatic ulcers	0.33 (0.01, 8.14)	Meta-RCTs
	Serious CV or renal events	0.53 (0.08, 3.46)	Meta-RCTs
NSAID +PPI vs NSAID	Serious GI complications	0.46 (0.07, 2.92)	Meta-RCTs
	Symptomatic ulcers	0.09 (0.02, 0.47)	Meta-RCTs
	Serious CV or renal events	0.78 (0.10, 6.26)	Meta-RCTs
Cox-2 inhibitors +PPI vs Cox-2 inhibitors	Recurrent ulcer bleeding	8.9% vs 0%	RCT
	GI hospitalisation	0.69 (0.52, 0.93)	CS
NSAID +misoprostol vs NSAID	Serous GI complications	0.57 (0.36, 0.91)	Meta-RCTs
	Symptomatic ulcers	0.36 (0.20, 0.67)	Meta-RCTs
	Serious CV or renal events	1.78 (0.26, 12.07)	Meta-RCTs
	Diarrhoea	1.81 (1.52, 2.61)	Meta-RCTs

(Table continues on the next page)

Table 1.3: Side effects associated with pharmacological therapies. Adapted from Zhang, 2010 (cont.)

Intervention	Adverse events	RR/OR (95% CI)	Evidence
<u>Cox-2 inhibitors</u>			
Coxibs vs NSAID	Serious GI complications	0.55 (0.38, 0.80)	Meta-RCTs
	Symptomatic ulcers	0.49 (0.38, 0.62)	Meta-RCTs
	Serious CV or renal events	1.19 (0.80, 1.75)	Meta-RCTs
Celecoxib	Myocardial infarction	2.26 (1.00, 5.10)	Meta-RCTs
	Myocardial infarction	0.97 (0.86, 1.08)	Meta-CSs/CCs
Rofecoxib	Myocardial infarction	2.24 (1.24, 4.02)	Meta-RCTs
	Myocardial infarction	1.27 (1.12, 1.44)	Meta-CSs/CCs
Valdecoxib	CV events	2.30 (1.10, 4.70)	Meta-RCTs
Opioids	Any	1.40 (1.30, 1.60)	Meta-RCTs
	Constipation	4.08 (3.30, 5.05)	Meta-RCTs
	Nausea	3.15 (2.68, 3.72)	Meta-RCTs
	Vomiting	5.99 (4.20, 8.54)	Meta-RCTs
	Dizziness	3.74 (3.00, 4.66)	Meta-RCTs
	Somnolence	4.78 (3.65, 6.26)	Meta-RCTs
Glucosamine	Any	0.97 (0.88, 1.08)	Meta-RCTs
Chondroitin sulphate	Any	0.99 (0.76, 1.31)	Meta-RCTs
Diacerhein	Diarrhoea	3.51 (2.55, 4.83)	Meta-RCTs
IAHA	Local adverse events	1.49 (1.21, 1.83)	Meta-RCTs
IA high molecular HA (Hylan)	Flares of pain and swelling	2.04 (1.18, 3.53)	Meta-RCTs

Abbreviations: CC: case-control study; CS: cohort study; PPI: proton pump inhibitor; H₂-blockers: histamine type 2 receptor antagonists; CV: cardiovascular; IA: intra-articular.

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Overall, the effects of agents used to treat OA vary, from small to moderate.

Many of the pharmacological therapies have increased risk of side effects associated with their use, and some of the side effects are serious, while most of the therapies listed in Table 1.2 are not disease-modifying.

Therefore there is enormous scope for the development of additional effective therapies for OA, especially those which also modify structural progression.

1.5.3 Emerging bone–active treatments for musculoskeletal pain

New treatments are emerging for musculoskeletal pain using anti–resorptive bone agents. These have been reviewed briefly by Zhang (2010), but the field is moving quickly and numerous relevant studies post–date Zhang’s review.

Interest in the field followed Carbone’s (2004) observational study regarding the effect of various antiresorptive drugs (oestrogen, raloxifene, and alendronate) on structural findings and symptoms of knee OA amongst postmenopausal women (Carbone, 2004). They found that BMLs were significantly less common in alendronate users (OR 0.11; $p \leq 0.05$) compared to women not using any anti–resorptive agents.

Table 1.4 on page 60 shows experimental studies that investigated the effect of a bisphosphonate use on participants with OA and displays pain and structural outcomes (other outcomes not shown). Study quality, site of joint pain, duration of follow up and outcomes studied vary; few studies specifically investigated the effect of bisphosphonates on structural outcomes as well as pain. There is variation between the effect of different bisphosphonates on pain and structure; therefore beneficial effects may be limited to some bisphosphonates rather than being a class effect.

Risedronate is the medication studied in the largest number of patients in good quality trials (Table 1.4). Risedronate (15 mg daily) reduced markers of cartilage degradation and bone resorption, but differences in pain, radiological JSN, JSW or osteophyte formation were not statistically significant (Spector, 2005; Bingham, 2006). Other work demonstrated that risedronate 50 mg weekly may prevent an increase in BML size over 24 months (Raynauld, 2008) although this did not reach statistical significance.

Alendronate use had no effect on WOMAC outcomes after six months, and this study did not assess any structural outcomes (Jokar, 2010), and Fujita (2009) found no difference between the alendronate arm and participants receiving calcium alone. However, there are data suggesting it retards spinal osteophyte progression (Neogi, 2008). Fujita (2009) identified beneficial effects of etidronate compared to the calcium only group, but did not have any structural endpoints.

Aside from bisphosphonates, there have been several studies with OA endpoints using other medicines with well-described effects in bone, but without clear structure modification targets eg BMLs. There are open-label studies, such as one trial for treatment of knee OA with calcitonin (Esenyel, 2012). Two double-blind, placebo-controlled RCT's studies have assessed the effect of strontium; one in spine OA (Bruyere, 2008) and one in knee OA (Reginster, 2012). Bruyere (123) (124) (124) demonstrated that strontium was effective in improving back pain (using a 5 point Likert scale) and reducing disc space narrowing compared to placebo (Bruyere, 2008). A similar trial has been completed in knee OA, demonstrating statistically significant reductions in structural and pain endpoints, with reduction in knee JSN of 0.10mm (2g/day group), proportion of radiological progressors, markers of cartilage breakdown and WOMAC pain scale (3 units) compared to placebo over three years. Observed reductions in VAS of 3.01mm (2g/day) did not quite reach statistical significance. Importantly, this result is well below the reductions required for clinically significant reductions of pain (15mm), and persistence of patients to the three year endpoint was poor (58%) (Reginster, 2012), indicating the difficulty of maintaining patients on

treatment regimens over long periods of time, and the possibility of bias in the study.

These agents have all been licensed for use for other indications for some time, and the side–effect profiles observed in these studies were consistent with those recorded in previous studies (Bruyere, 2008; Reginster, 2012; Jokar, 2010; Spector, 2005; Bingham, 2006).

Therefore, the use of bone–active pharmacological agents for treatment of pain in OA and also structural modification is an exciting development in the field.

Table 1.4: Experimental studies of bisphosphonates in patients with osteoarthritis, sorted by site and year of publication

Study	Intervention and dose	vs	Population	Site	Study design	Placebo	Sample size	Duration	Pain outcomes	Structural outcomes
Saviola (2012)	Clodronate 300mg IV	Hydroxy–chlorquine 400mg loading dose, 200mg at 3 months	Erosive hand OA, VAS pain $\geq 4/10$, aged 45-75	Hand	RCT (open label)	No	38	24 months	VAS $p=0.03$ after 3 months	–
Spector (2005)	Risedronate 5mg/day; 15mg/day	Placebo	ACR–defined knee OA, daily knee pain, aged 40–80	Knee	RCT	Yes	284	12 months	WOMAC (ns)	JSN ($p=0.28$)
Bingham (2006)	Risedronate 5mg/day; 15mg/day; 50mg/week	Placebo	ACR–defined knee OA, knee pain on most days, medio-tibial mJSW 2–4 mm, aged 40–80	Knee	RCT	Yes	2483	24 months	WOMAC $p=0.66$	JSW ($p=0.98$)
Kawasaki (2008)	Risedronate (2.5mg/day + exercise)	Glucosamine + exercise vs exercise alone	ACR–defined knee OA, post–menopausal women	Knee	RCT (open label)	No	142	18 months	WOMAC (ns), VAS (ns) [§]	JSW (ns) [§]
Rossini (2009)	Clodronate (IA) 0.5 mg/week; 1mg/week; 2 mg/week, 2 x 1mg/week	Hyaluronic acid (20mg / week)	ACR–defined knee OA, KL grades 2–3, symptoms ≥ 3 months	Knee	RCT (open label)	No	145	5 weeks	VAS (ns)	–
Jokar (2010)	Alendronate 70 mg weekly	Placebo	ACR–defined knee OA, WOMAC pain score 2/5 & daily knee pain for ≥ 6 mo.	Knee	RCT	Yes	39	6 months	WOMAC $p= 0.94$	–

Table continues on next page

Table 1.4: Experimental studies of bisphosphonates in patients with osteoarthritis, sorted by site and year of publication (cont.)

Study	Intervention and dose	vs	Population	Site	Study design	Placebo	Sample size	Duration	Pain outcomes	Structural outcomes
Fujita (2001)	Etidronate 66 mg/day; 133 mg/day; 200 mg/day	No treatment	Back and/or knee pain due to spondylosis deformans and/or knee OA	Knee, spine	RCT, stratified by age, disease severity	No	80	12 months	VRS p<0.001; skin impedance p<0.001 between no treatment and all doses	-
Fujita (2009)	Alendronate 5 mg/day; etidronate 200 mg/day (ave.) risedronate 2.5 mg/day + calcium	Calcium alone 900 mg/day, for 7 months	Back or knee pain	Knee, spine	RCT	No	199	7 months	VRS, skin impedance p<0.001 between etidronate and calcium alone, others ns.	–

Results listed as not significant (ns) if paper does not state p value.

JSN: joint space narrowing; JSW: joint space width

[§]Comparison is for risedronate vs exercise alone

VRS: Visual rating scale

KL grade: Radiographic criteria for assessment of osteoarthritis using the Kellgren and Lawrence (KL) grading system

IA: intra-articular

ave: average

1.6 Summary

Arthritis is the most common cause of chronic pain in older people, affecting more than 6.3 million Australians. The most recent estimates suggest that arthritis and musculoskeletal conditions constituted the fourth largest component of direct health expenditure, costing the Australian economy AUD\$4.0 billion annually.

Correlates of pain are not consistent across all joints, but include obesity, weak muscles, pain in other joints and numerous structures visible on MR imaging, including bone marrow lesions, cartilage defects, meniscal tears, osteophytes (but not independently of MRI changes), joint effusions, and synovitis. Features visible only on radiographs (eg joint space narrowing) are poorly correlated with pain. Cognitive, psychological, and psychosocial aspects also influence pain, with causality also working in the opposite direction, with evidence that osteoarthritic knee or hip pain determines subsequent depressed mood through its effect on fatigue and disability.

Treatment options for modifying musculoskeletal pain include non-pharmacological treatments, such as weight loss, physical activity, and lifestyle modification. Pharmaceutical treatments include oral paracetamol, NSAIDs, COX-2 inhibitors, glucosamine sulphate, chondroitin sulphate, capsaicin, injections of corticosteroids, glucosamine, chondroitin sulphate, and weak opioids. Once conservative measures have failed, surgical treatments such as joint replacements may be considered. The effect of treatment from available therapies remains suboptimal, and although existing treatments are safe options, all pharmacological and surgical treatments have side effects and risks. There is scope in the current treatment

armamentarium for more effective therapies, and even for treatments with smaller effect sizes that can be taken in addition to existing medications as long as they are safe. Treatments remain symptom modifying but not truly disease modifying. An agent that achieves symptom modification and disease modification remains the “holy grail” for OA treatment.

Chapter 2: Research questions

Chapter 2. Research questions

2.1 Research questions

Research questions 1 and 2 investigate correlates and one determinant of musculoskeletal pain.

In a population-based cohort of community-dwelling adults aged 50–80 years examined at baseline and 2.6 and 5 years later:

1. What is the relationship between osteoarthritis and health-related QoL over five years?
 - 1.1. Is the relationship between these factors the same cross-sectionally as it is longitudinally (over 2.6 and five years)?
 - 1.2. What is the contribution of physician diagnosed OA, radiographic measures of knee OA and pain at multiple sites to QoL?
2. Is there an association between baseline 25-hydroxyvitamin D (25-OHD) at baseline, and change in knee pain over 5 years and change in hip pain over 2.6 years, as measured by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire?
 - 2.1. If there is an association, what is the nature of that association? Is the association linear or is there a threshold?
 - 2.2. Is the relationship consistent within WOMAC subscales?

Research questions 3 and 4 investigate modifiers of musculoskeletal pain using two different treatment modalities in double-blind randomised-controlled-trials.

3. Is a thrice daily application of topical 4Jointz 3.5 g/day (compared to placebo), effective in reducing knee pain, improving muscle strength and markers of inflammation and cartilage breakdown over twelve weeks in participants aged >50 with OA and a pain intensity score >40mm on a visual analogue scale (VAS)?

3.1. Does this effect reverse over four weeks after discontinuation of 4Jointz (compared to placebo)?

4. Is a single infusion of zoledronic acid 5mg (compared to placebo) effective in reducing knee pain and BMLs over twelve months in participants aged ≥ 50 years with ACR-defined clinical knee OA, pain on most days and a pain intensity score of >40mm on a visual analogue scale (VAS) and a prevalent knee BML?

4.1. If there is a reduction in areal BML size, is it sufficient to expect that this is the mechanism for the pain reduction?

Chapter 3: Methodology

Chapter 3. Methodology

3.1 Prelude

Two chapters of this thesis utilise data from the Tasmanian Older Adult Cohort (TasOAC) study. This chapter describes the study design, study population, and measurement protocols which are common to these two chapters.

Please note that the following data chapters are presented in the form in which they were accepted by, or submitted to peer-reviewed scientific journals. Therefore there are some differences in the way aspects of the TASOAC study are described, based on requirements of different journals and the emphases required for different analyses. The sample sizes used in individual chapters varies for each of the research questions.

Chapters 6 and 7 describe the two intervention trials of this thesis – 4Jointz and ZAP. These are both placebo-controlled double-blind randomised controlled trials in patients with clinical knee OA. Study-specific methodologies for these two trials appear in these two chapters.

3.2 TASOAC design and study population

TASOAC is an ongoing prospective, population-based study which aimed to identify the environmental, genetic and biochemical factors associated with the development and progression of osteoarthritis (OA) and osteoporosis at multiple sites (hand, knee, hip, spine).

The TASOAC sample consists of men and women aged 50-80 years (mean age 62 ± 7 years), selected from the roll of electors in southern Tasmania (population 229,000) using stratified simple random sampling without replacement. Stratification was by sex, enabling equal numbers of men and

women to be enrolled. The electoral roll represents the most complete population listing of Australian adults available, as voting is compulsory in state and federal elections. As TasOAC was designed to examine community-dwelling older adults, institutionalised older adults were excluded from the initial sample. Participants were also excluded if they had contra-indications for MRI (including pacemakers, implants and claustrophobia), as MRI was required to examine OA progression. Other exclusion criteria included body weight exceeding the weight limit on the dual energy X-ray absorptiometry (DXA) machine (>135 kg), and inability to come to the clinic (for example, if they resided interstate or overseas, see Figure 3.1).

3.2.1 Ethics

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the study (Ethics Approval Number: H6488), and we obtained written informed consent from all participants.

3.2.2 Baseline (Phase 1)

An overview of participant recruitment and withdrawal during the baseline phase of TASOAC is shown in Figure 3.1. 2530 people were identified from the electoral roll, of which 2135 were identified as initially eligible. Of the people who did not take part in the study, 395 people were identified as not being eligible, with the most common reasons being claustrophobia, too sick, or living overseas or interstate. 231 people were not able to be contacted, 804 did not want to enter the study, and one participant failed to attend the clinic. The remaining 1099 people attended the clinic at the Menzies Research Institute Tasmania from February 2002 to September 2004.

The overall response rate for participation in Phase 1 is 57%, which is similar to response rates from studies with equivalent response burdens conducted

around the same time period, such as the North West Adelaide Health Study at 58% (Grant, 2009), and the Australian Diabetes, Obesity and Lifestyle Study at 52% (Dunstan, 2002).

Figure 3.1 provides an overview of participant recruitment into Phase 1.

Participants in TASOAC completed questionnaires on a wide range of demographic factors, as well as a number of specific questionnaires including knee pain and stiffness and quality of life. Participants also attended clinic at the Menzies Research Institute Tasmania and supplied a fasting blood sample, and had other measures taken in person, such as blood pressure and leg strength. Participants also attended appointments for bone density testing (using dual energy X-ray absorptiometry (DXA)), radiography, and magnetic resonance imaging).

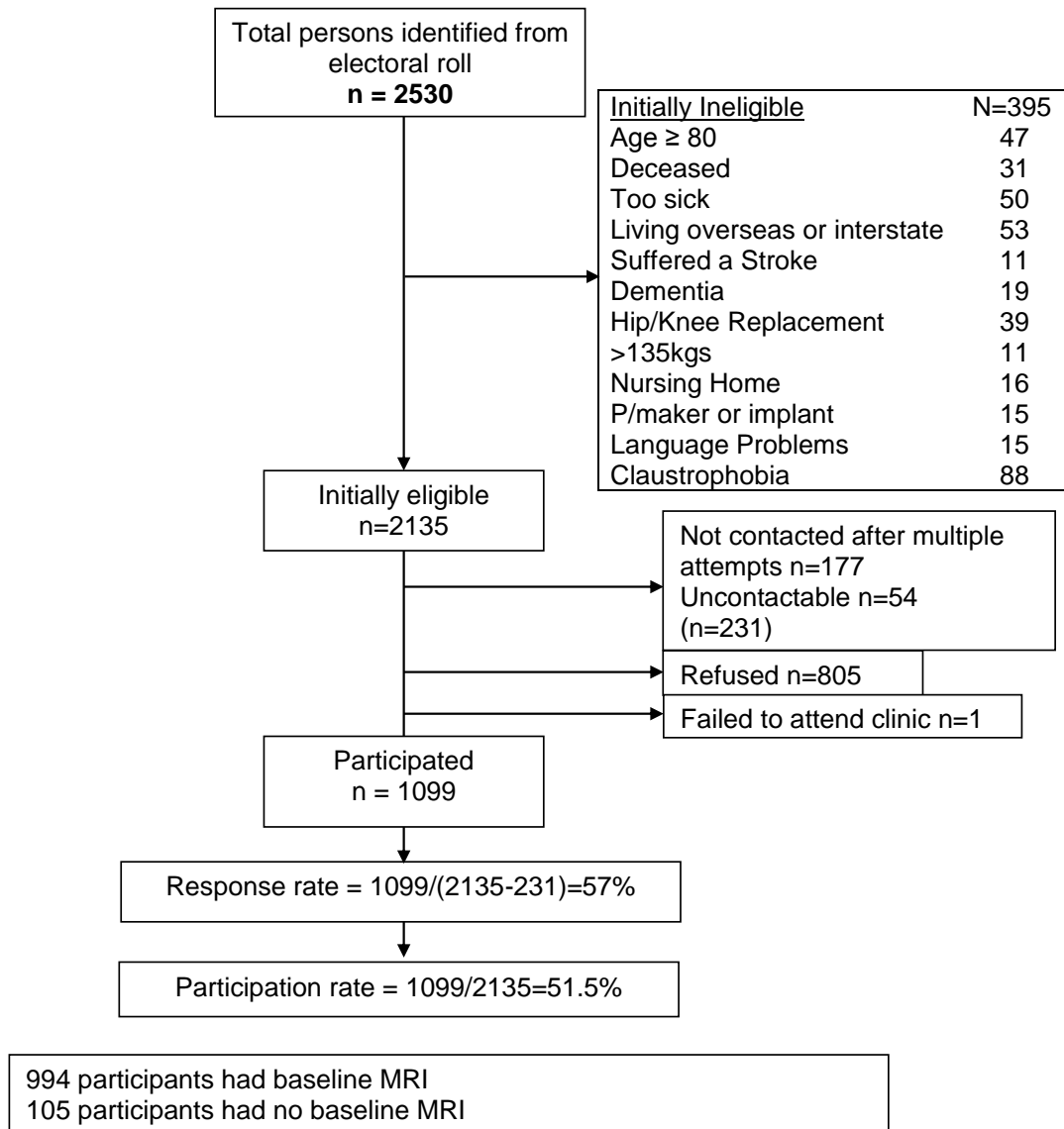


Figure 3.1: Flow chart of TasOAC recruitment and participation to end of Phase 1

Table 3.1 shows that TASOAC participants (n=1099) were representative of the 2530 people selected from the electoral roll with regard to sex, (48.9 % male vs 50.7% male), and also regard to age for the middle and younger third of the cohort (born 1933 – 1945 and 1943 – 1952). However, the older age group (born 1921 – 1933) were under-represented in the 1099 participants who provided baseline measures (21.4% vs 39.8% and 35.9% for the younger groups).

Table 3.1: Baseline demographic characteristics of those participants who completed Phase 1 (n=1099) and those who did not (n=1431)

	Did not participate in Phase 1 n=1431	Participated in Phase 1 n=1099	p
Sex (% Male)	50.7	48.9	0.37
Age group			
1921-1933	486 (34.0)	235 (21.4)	<0.001
1933-1945	473 (33.1)	437 (39.8)	
1943-1952	423 (29.6)	394 (35.9)	

Age group 1921 - 1933 consists of persons in the age groups "1921-1925" "1923-1927" "1925-1929" "1928-1932" and "1929-1933".

Age group "1933 - 1945" consists of persons in the age groups "1933-1937" "1937-1941" "1938-1942" and "1941-1945".

Age group "1942 - 1952" consists of persons in the age groups "1943-1947" "1945-1949" "1948-1952".

3.2.3 2.6 year follow up (Phase 2)

Participants were contacted and asked to return for subsequent visits after 2–3 years (mean \pm SD 2.6 ± 0.4 ; range 1.4–4.8 years). The majority of the 1099 participants who took part in Phase 1 returned for Phase 2 (80%, see Figure 3.2). As TASOAC aimed to measure osteoarthritis progression, participants without baseline MRI were excluded from Phase 2. The other common reasons for patients discontinuing involvement in the study after Phase 1 were not wanting to continue in the study.

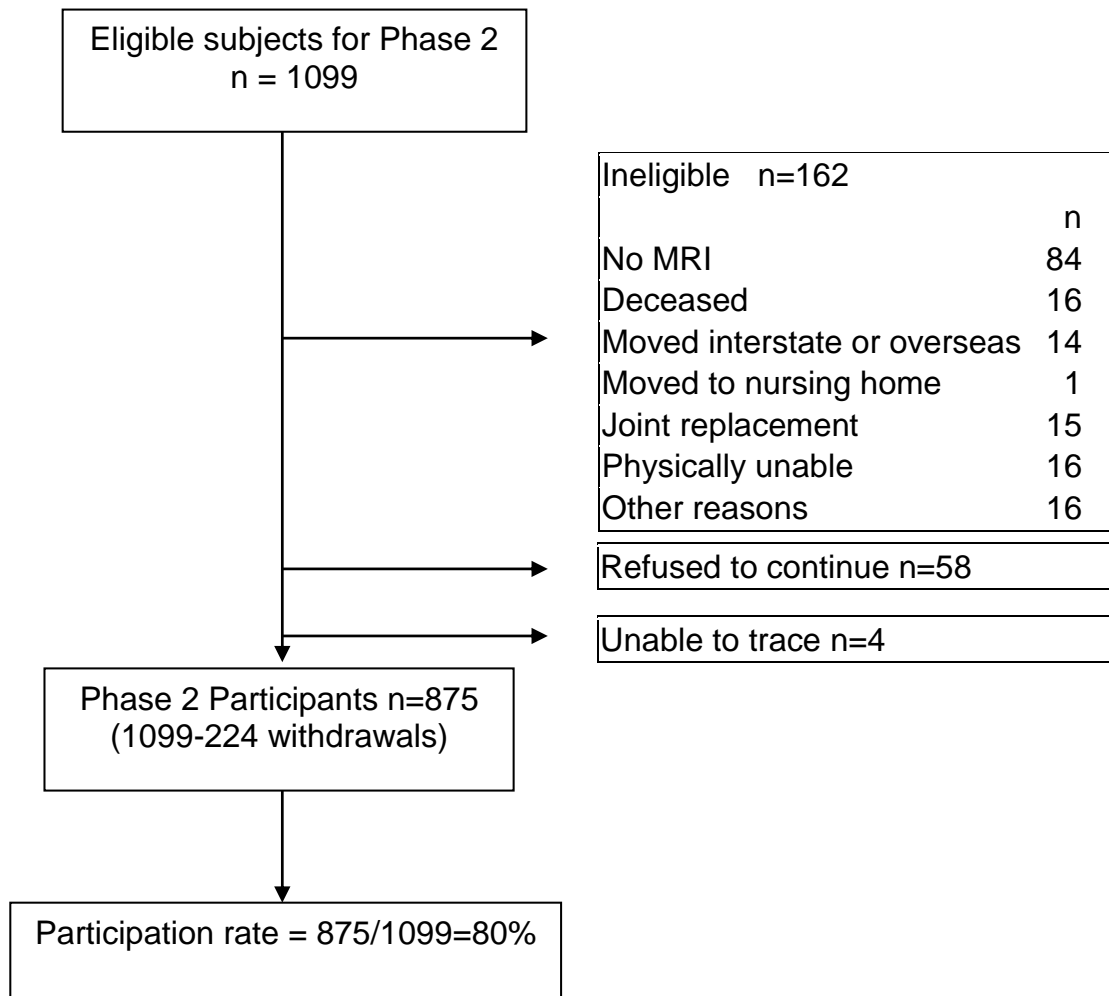


Figure 3.2: Flow chart describing participation in Phase 2 of TASOAC

TASOAC participants who did not complete Phase 2 were older, more likely to be female, shorter and had higher BMI than participants who completed both Phase 1 and Phase 2 (Table 3.2).

Table 3.2: Baseline demographic characteristics of those participants who completed Phase 2 (n=875) and those who did not (n=224)

	Participated in Phase 2 (n=875)	Did not participate in Phase 2 (n=224)	p value
Age (years)	62.7 (7.3)	64.4 (8.2)	<0.01
Male sex (n, %)	445 (51)	92 (41)	<0.01
Height (cm)	167.5 (9.0)	164.9 (8.8)	<0.01
Weight (kg)	77.9 (14.6)	77.7 (16.5)	0.824
BMI (kg/m ²)	27.7 (4.6)	28.5 (5.7)	0.040

Bolded results indicate statistically significant difference at $\alpha=0.05$

*Mean (standard deviation) except for percentages. *P* values determined by t-test or chi-square test (where appropriate). BMI: body mass index.

3.2.4 Five year follow up (Phase 3)

Participants who completed Phase 2 were invited to continue participation in the study for Phase 3, which occurred 5 years after Phase 1 (mean \pm SD 5.05 ± 0.5 ; range 3.6 – 6.9 years).

The most common reasons for patients to discontinue involvement in the study after Phase 2 were refusing to continue, physical inability to attend, and death (see Figure 3.3).

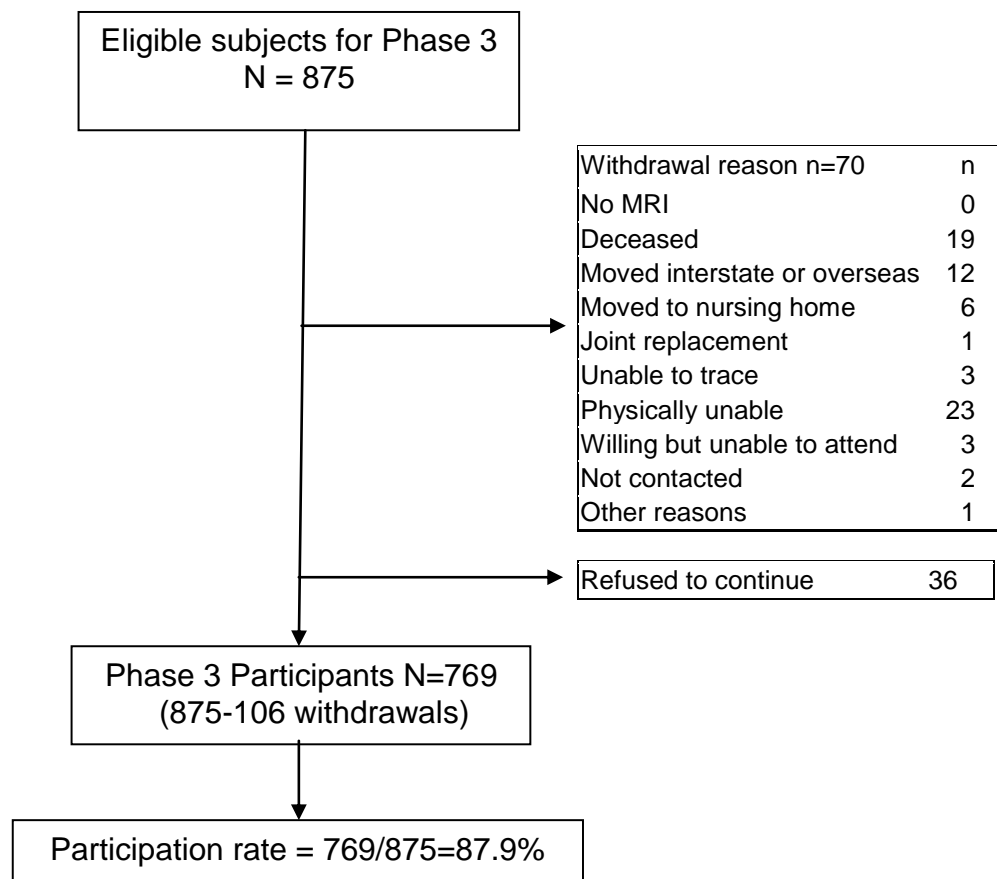


Figure 3.3: Flow chart describing participation in Phase 3 of TASOAC

Those completing Phase 3 were younger, taller and had lower BMI at baseline than participants who did not complete Phase 3 (Table 3.3). This includes participants who dropped out before Phase 2.

Table 3.3: Characteristics of study cohort at baseline in participants who did and did not complete Phase 3

	Participated in Phase 3 Mean (sd) n=769	Did not participate in Phase 3 Mean (sd) n=330	p value
Age (years)	62.1 (7.0)	65.2 (8.1)	<0.001
Sex (% male)	49.5	54.8	0.110
Height	167.5 (8.9)	165.7 (9.2)	0.003
Weight	77.8 (14.6)	78.1 (15.8)	0.747
Body mass index	27.7 (4.6)	28.4 (5.1)	0.02

Bolded results indicate statistically significant difference at $\alpha=0.05$

*Mean (standard deviation) except for percentages. *P* values determined by t-test or chi-square test (where appropriate). BMI: body mass index.

3.3 Measurement of pain

Functional MRI (fMRI) is an MRI procedure that measures brain activity by detecting associated changes in blood flow. fMRI scans show altered processing of the affective qualities of the ongoing pain (Baliki, 2008; Kulkarni, 2007; Parks, 2011), and should give the actual pain patients experience (as compared to what they report), as well as answering important questions about the nature of pain in patients with osteoarthritis. Therefore, this represents the gold standard of pain measurement in an ideal world, but fMRI and other brain imaging techniques are limited to specialised use and are not currently used as outcome measures in clinical trials or epidemiological studies.

Pain questionnaires and visual analog scales are the usual methods of assessing pain intensity due to good reliability, validity, sensitivity to change and ease of use, but the potential for under– or over–reporting of pain intensity remains. This may be systematic in nature, and so this limitation needs to be considered in data interpretation.

Questionnaire–based methods of assessing musculoskeletal pain in adults can be divided into several categories (Hawker, 2011). These include:

- generic unidimensional pain questionnaires (visual analog scale and numeric rating scale);
- generic multidimensional pain questionnaires (Short Form–36 Bodily Pain Scale);
- arthritis–specific pain questionnaires (Measure of Intermittent and Constant Osteoarthritis Pain) (Hawker, 2008); and

- composite measures of arthritis symptoms, including pain and associated disability or dysfunction, such as the Western Ontario and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos, 1998) and McMaster Universities Osteoarthritis Index (Bellamy, 1988).

In this thesis, we have used visual analog scales, WOMAC and KOOS questionnaires to assess pain intensity.

3.4 Study populations

Participants from TASOAC are utilised in two chapters – Chapter 4 and Chapter 5. A summary of when measures were assessed over all three Phases is shown in Table 3.4 on page 89. This is not an exhaustive list of all the measures which were actually taken in TASOAC.

Chapter 6 and Chapter 7 utilise study participants recruited into the 4Jointz and ZAP trials rather than TASOAC. Characteristics of the study participants are presented in each of these chapters.

Study populations are summarised in Table 3.6 on page 91.

3.5 Study measures

Details of how outcome measures and covariates were assessed are described below. Study measures appear here in Chapter 3 if they were used in multiple studies or where space restrictions precluded full description of methods in published papers. The location of methods descriptions for particular outcomes, predictors or covariates are shown in Table 3.5 on page 90.

3.5.1 Anthropometrics

Body weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707, Bradford, MA, USA). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as $\text{weight (kg)} / (\text{height (m)})^2$. Waist and hip circumference were measured to the nearest 0.1 cm using a constant tension tape (Figure Finder Tape Measure) directly over the skin.

3.5.2 Questionnaire measures

3.5.3.1 Highest educational attainment

At baseline, participants were asked “What is the highest qualification you have completed?”. Participants could select one answer only. Response options are as follows: “No formal qualifications”; “School or Intermediate certificate (or equivalent)”; “Higher School or Leaving Certificate (or equivalent)”; “Trade/apprenticeship (eg Hairdresser, Chef, Motor Mechanic)”; “Certificate/diploma (eg Child Care, Technician, Nursing, Chartered Accountant)”; “University Degree”; “Higher University degree”.

3.5.3.2 Current employment status

At baseline, participants were asked “Which of the following best describes the occupation you had for the longest period?”. Response options were as follows: “Manager or administrator”, “Professional (eg engineer, doctor, teacher, nurse, police officer, technical officer)”, “Tradesperson (eg carpenter, electrician, plumber, book keeper, etc)”, “Salesperson or personal service worker (eg sales rep., teller, insurance rep, real estate rep., etc)”, “Plant or machine operator, or driver (eg taxi or bus driver, etc)”, “Clerk (eg typist, receptionist, data processor, bookkeeper, etc)”, “farmer”, “Labourer or related worker (eg trade assistant, factory hand, agricultural labourer, construction, mining)”, “Member of armed forces”, or “other”.

3.5.3.3 Self-reported arthritis, as diagnosed by a physician

Participants were asked about presence or absence of physician–diagnosed osteoarthritis and pain at baseline at the neck, back, hands, shoulders, hips, knees, or feet (yes / no options – see Appendix 1)), and physician–diagnosed rheumatoid arthritis (RA) (yes / no).

3.5.3.4 *Self reported pain*

Similarly, participants were asked whether joint pain was present or absent at seven different joints: neck, back, hands, shoulders, hips, knees, or feet (see Appendix 1).

3.5.3.5 *Cigarette smoking*

Self-reported estimates of smoking status (never, former, and current) was determined by questionnaire from the following questions “Have you ever smoked cigarettes on a regular basis?”; “Do you currently smoke cigarettes?”, and “If you have given up smoking, at what age did you stop?” (see Appendix 1). Participants were considered a current smoker if they reported currently being a “regular smoker”.

3.5.3.6 *Alcohol consumption*

Alcohol consumption was assessed by a validated food frequency questionnaire (FFQ) which was developed specifically for use in Australian adults (Hodge, 2000). Participants were asked about their average alcohol consumption over the past 12 months. The consumption frequency of each alcohol type [beer (low alcohol); beer (full strength); red wine; white wine (includes sparkling wines); fortified wines, port, sherry, etc.; and spirits, liqueurs, etc.] was asked about separately. An estimated daily intake of alcohol (gram/day) was calculated.

3.5.3.7 *Western Ontario McMaster Osteoarthritis Index (WOMAC)*

Self-reported knee and hip pain, function and stiffness were assessed by questionnaire for the last 30 days using the Western Ontario McMaster Osteoarthritis Index (WOMAC) (Bellamy, 1988) (see Appendix 1). The WOMAC pain scale has five items, each rated on a 10-point scale from 0 (no pain) to 9 (most severe pain). Lower scores indicate lower levels of symptoms or physical disability. Each pain item was summed to create a

total pain (0–45) score. The WOMAC index has good test–retest reliability, with values of 0.68 for the pain scale and 0.48 for the function scale (Bellamy, 1988), and has demonstrated convergent construct validity over numerous impairments (McConnell, 2001). Responsiveness of the WOMAC is variable depending on the intervention measured (McConnell, 2001), as expected.

3.5.3 Strength and physical activity measures

3.5.3.1 Muscle strength

Leg strength was measured to the nearest kilogram in both legs simultaneously, using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Participants stood on the back of the dynamometer platform, with back straight against a wall and knees flexed to an angle of 115° from the neutral angle of full extension (dependent on participant range of motion). A demonstration of the leg strength assessment technique is provided in Figure 3.4. A bar connected by a chain to the dynamometer was held on the front of the thighs with both hands. Using only their legs and keeping the back and neck straight, the participant was then instructed to lift the bar upwards with maximum force, and given verbal encouragement until a maximal contraction was achieved. This test examines isometric strength of the whole legs, but predominantly of the quadriceps and hip extensors.

Two trials were recorded, with the mean score taken as the criterion value for leg strength. A third trial was performed if the score for the first two trials varied by more than 10% (Kumar, 2004). Intra–class correlation coefficients (ICC's) demonstrated high reproducibility between trials 1 and 2 at both baseline (ICC 0.95, 95% CI 0.94, 0.96) and follow–up (ICC 0.96, 95% CI 0.95, 0.97).

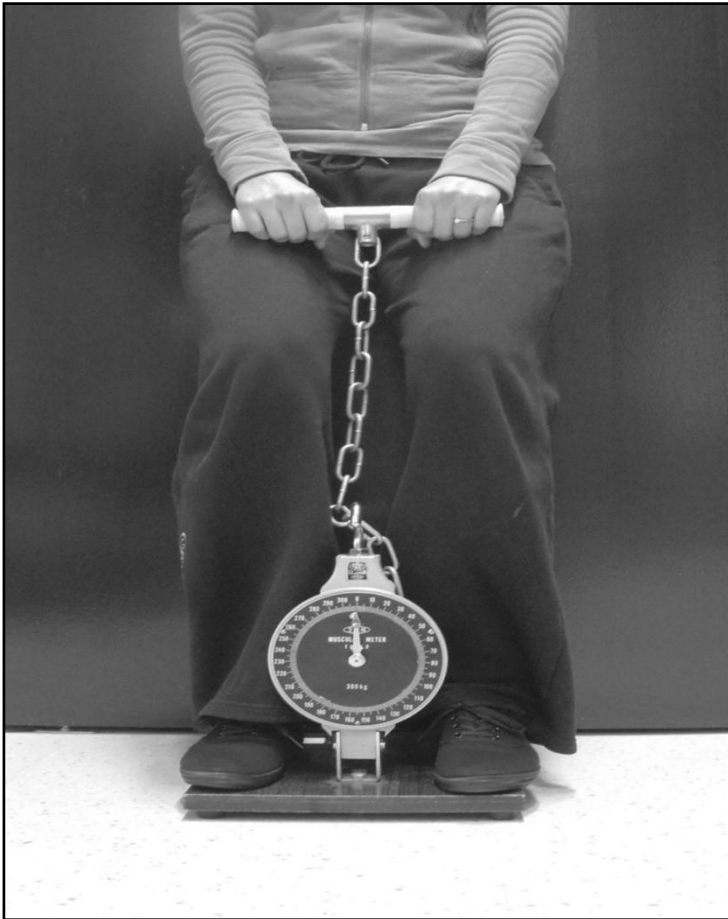


Figure 3.4. Demonstration of the leg strength test performed in the TASOAC study (from Scott, 2010).

This measure of muscle strength has not been validated, but quadriceps strength as measured by isokinetic knee extension strength tests used in falls risk assessment has been previously demonstrated to be a predictor of pain, (Zhai, 2006) falls (Lord, 1999), disability (McAlindon, 1993) and mortality (Newman, 2006) using similar tests. Knee extension strength in our participants at all points was strongly correlated with leg strength ($r = 0.77$ at Phase 1, $r = 0.73$ at Phase 2 and $r = 0.73$ at Phase 3, all $p < 0.0001$) providing reassurance about our leg strength measure. We chose not to include knee extension strength in our analyses due to a “ceiling effect” in that approximately 20% of participants achieved the maximum reading of 46kg at

each of the three time points, and also because it assesses strength over the whole leg rather than predominantly the quadriceps.

3.5.3.2 Pedometers

Physical activity levels were assessed as steps per day using pedometers (Omron HJ-003 and HJ-102; Omron Healthcare, Kyoto, Japan).

Pedometers were calibrated at the clinic with the participant present, using a 100–pace walking test. Participants were shown how to attach the pedometers to their waistband or belt and were instructed to wear the pedometer above their dominant leg. Pedometers were calibrated at the clinic with the participant present, using a 100–pace walking test.

Participants were provided with a pedometer diary and were instructed to record their steps daily for seven consecutive days from the following day.

Participants were mailed out a second pedometer after a six month period and repeated the process. A steps per day value was calculated which was the daily average of these two time periods. The start and the finish times of pedometer use were recorded on each day, and participants also reported the duration and the type of physical activity for any periods in which they did not wear the pedometer. Pedometer readings were excluded if they were determined to be caused artificially (eg report of work done on heavy machinery), or if the pedometer had been worn for less than five days and for less than eight hours on each of these days, excluding reported duration of pedometer removal.

3.5.4 X-ray

Participants had X-rays of both hips (n=1014) and knees (n=1020) in the standing antero–posterior position at baseline only. Knee X-rays were taken of both knees with 15° of fixed knee flexion, and pelvic radiographs with both

feet in 10° internal rotation. Films were scored individually for osteophytes and joint space narrowing (JSN) on a scale of 0–3 (where 0=no disease and 3=most severe disease) according to the Osteoarthritis Research Society International (OARSI) atlas as previously described (Altman, 1995). This is also referred to as “OARSI grade”. Hips and knees with scores 1–3 at any site were classified as having JSN or osteophytes. Two readers simultaneously assessed radiographs with immediate reference to the atlas. Scores for each participant were determined by consensus. Intraobserver repeatability was assessed in 40 participants (intraclass correlation coefficients (ICCs) 0.65 to 0.85 for the knee and 0.60– 0.87 for the hip) (Foley, 2006).

Table 3.4: Summary of when measures were assessed in the TASOAC study

Measure	Baseline (Phase 1) n=1099	2.6 years (Phase 2) n=875	5 years (Phase 3) n=769
Questionnaire items			
Occupation	✓		
Employment status	✓	✓	✓
WOMAC scale			
Knee pain	✓	✓	✓
Hip pain		✓	✓
Pain at any of these sites – neck, back, hands, shoulders, hips, knees, feet,	✓	✓	✓
Osteoarthritis diagnosed by a doctor (y/n) at neck, back, hands, shoulders, hips, knees, feet	✓	✓	
Smoking survey	✓	✓	✓
Ever been diagnosed by a doctor (y/n) with rheumatoid arthritis	✓	✓	✓
Current medications (dosage, frequency) including prescription and over the counter medications	✓	✓	✓
Dietary questionnaire (FFQ), including alcohol intake	✓	✓	✓
AQOL	✓	✓	✓
Clinic measurements			
Blood taken (vitamin D)	✓	✓	
Height, weight, girth (hip and waist)	✓	✓	✓
Pedometer (7 days of wear at 2 time points 6 months apart)	✓	✓	✓
Leg strength	✓	✓	✓
X-ray			
Hip	✓		
Knees	✓		✓
MRI			
Knee	✓	✓ (n=425)	
Hip	✓	✓	✓
	(n=151)	(n=323)	(n=220)

Note: This is not an exhaustive list of all the measures taken in TASOAC, only the most relevant.

3.6 Summary of outcome factors, study factors, and covariates

Table 3.5 summarises the variables used in each chapter of this thesis.

Table 3.5: Summary of outcome factors, study factors, and covariates used in this thesis

Chapter	Outcome factors	Study factors	Covariates
4	Quality of life (AQoL)*	Self-reported physician–diagnosed osteoarthritis, self-reported joint pain (yes / no), knee osteophytes, knee joint space narrowing	Self-reported physician diagnosed rheumatoid arthritis, leg strength, age, sex, BMI
5	Serum 25-OHD (Vitamin D)*	WOMAC knee and hip pain	Age, sex, BMI, season, leg strength, hip joint space narrowing, osteophytes, number of cartilage defects, presence of knee bone marrow lesions
6	Knee pain (VAS)*, KOOS pain scale; knee function*; IL-6*, CTX-2*, OMERACT–OARSI response criteria*; paracetamol use*; leg strength; adverse events*	Randomised to receive 4Jointz or placebo	OARSI grade, sex
7	Knee pain (VAS)*, KOOS pain scale*; bone marrow lesion size*, adverse events*	Randomised to receive zoledronic acid or placebo	Age, sex, baseline pain score, baseline pain medicine use

*Measurement protocol described in “Methods” or “Patients and Methods” section of relevant chapter.

AQoL: Assessment of Quality of Life instrument

OARSI grade: a classification of radiographic knee osteoarthritis

VAS: visual analog scale

IL-6: interleukin 6, an inflammatory marker

CTX-2: C-terminal cross linking telopeptide of type 2 collagen, a marker of cartilage tissue degradation

OMERACT–OARSI response criteria: responder criteria defined by the relevant professional societies

KOOS: Knee Injury and Osteoarthritis Outcome Score

Table 3.6. Study populations used in this thesis

Chapter	Study	Selection	Source	Recruitment location	Population	Year of data collection	Age [†]	n
4,5	Tasmanian Older Adult Cohort Study (TASOAC)	Random selection	Electoral roll	Southern Tasmania	Ambulant community dwelling	2002–08	50–80	P1:1099 P2: 875 P3: 769
6	A randomised controlled trial of Arthritis Relief Plus for osteoarthritis of the knee (4Jointz trial)	Convenience sample	Newspaper advertising, physician referral	Southern Tasmania, Sydney	Clinical knee OA, Knee pain on most days, VAS pain score ≥ 40 mm	2011	>50	133
7	Zoledronic acid in knee pain associated with bone marrow oedema (ZAP trial)	Convenience sample	Newspaper advertising, physician referral	Southern Tasmania	Clinical knee OA, Knee pain on most days, VAS pain score ≥ 40 mm, bone marrow lesion	2009–10	>50	59

[†]Age (years) at enrolment

VAS: visual analog score

P1, P2, P3: The three phases of TASOAC, phases 1, 2 and 3, representing baseline, 2.6 year follow up and 5 year follow up

3.7 Statistical analysis

T-tests and χ^2 tests were used to compare differences in means and proportions as appropriate. Statistical significance was determined using $\alpha=0.05$ and two –tailed tests throughout the thesis. Detailed descriptions of statistical analyses performed are presented in the relevant data chapters. All statistical analyses were performed on Stata 10 – 12 for Windows (StataCorp, College Station TX, USA).

Chapter 4: A prospective study of the
impact of musculoskeletal pain and
radiographic osteoarthritis on health related
quality of life in community dwelling older
people

Chapter 4. A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people

This manuscript has been published (Laslett *et al*/ BMC Musculoskelet Disord. 2012;13:168). The typeset version of the manuscript as it appeared in the journal is in Appendix 4.

The text of this chapter is the same as the published version, except where changes have been requested by the examiners. Therefore there is some repetition of the methods, some of which appear in more detail in Chapter 3.

4.1 Introduction

Quality of life (QoL) is a useful and widely-used measure of health status because it captures the personal and social context of patients' lives in a quantifiable way, and predicts use of health care resources and mortality (Dorr, 2006; Singh, 2005). Osteoarthritis (OA) is a leading cause of disability amongst older adults, and persons with osteoarthritis typically score poorly on QoL measures. Aspects of QoL involving physical functioning and pain are the most affected, and patients who report pain typically report it at more than one site (Croft, 2005). Number of sites of pain have been associated with increasing disability (Croft, 2005) and poorer overall health, sleep quality and psychological health (Kamaleri, 2008). However, it is unclear whether pain at different sites is additive in terms of effect on QoL. Radiographic markers of osteoarthritis are weakly associated with pain (Bedson and Croft, 2008; Hannan, 2000) but both are associated with poor QoL, and it is unclear if radiographic findings are independent of a diagnosis of OA, or pain (Kim, 2010;

Muraki, 2011; Norimatsu, 2011). In addition, it is not known whether the cross-sectional associations track over time. Baseline back, knee and hip pain were associated with reducing QoL over four years of observation in a Chinese volunteer cohort (Woo, 2009) but this has not been reported in western populations, in other anatomical sites, or in a population which also has radiographic measures.

The aim of this study was to describe the association between osteoarthritis and QoL in a community dwelling population-based sample of older people over five years.

4.2 Patients and methods

4.2.1 Participants

The Tasmanian Older Adult Cohort (TASOAC) is an ongoing, prospective, population-based study examining the determinants of osteoarthritis and osteoporosis in older community dwelling adults. Men and women aged 50–80 years in 2002 were selected from the electoral roll in Southern Tasmania (population 229,000) using sex-stratified simple random sampling without replacement (response rate 57%). Participants were excluded if they resided in an aged care facility. The research was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and written informed consent was obtained from all participants. Participants attended clinic and completed questionnaires. Data collection included blood sampling, magnetic resonance (MR) imaging (not reported in this study), knee and hip X-ray and other correlates of knee and hip OA and osteoporosis. Baseline data (Phase 1) was collected from February 2002 to September 2004. Follow up data (Phase 2 and 3) was collected on average 2.6 (range 1.4 to 4.8) and 5 years (range 3.6 to 6.9 years) later. Participants who did not have an MRI at Phase 1 (n= 105)

were excluded from further participation in the study, as TASSOAC aimed to measure osteoarthritis progression.

4.2.2 Quality of life

Health-related QoL was measured using the Assessment of Quality of Life (AQoL) questionnaire (Hawthorne, 2000). This is a generic QoL instrument with five subscales (Illness, Independent Living, Social Relationships, Physical Senses and Psychological Well-being), each with three items with four response levels (scored 0–3 for each item). The AQoL is a valid measure of QoL (Osborne, 2003) and is reliable in population-based settings (Cronbach's $\alpha = 0.81$) (Hawthorne and Osborne, 2005). The AQoL was used as an unweighted, psychometric instrument providing 'value' profiles, rather than using the utility measures (Hawthorne, 2000) such as the AQoL-4D. These use only four of the subscales, excluding the Illness subscale which includes questions about the use and reliance on prescribed medicines or medical aids and requirement for regular medical treatment, all of which are likely to be increased by pain or a diagnosis of OA. Total scores for each subscale therefore ranged from 0–9 and the total instrument 0–45, with higher scores in each scale indicating worse QoL.

4.2.3 Physician diagnosed osteoarthritis, pain and rheumatoid arthritis

Participants completed questionnaires (n=1099) which asked "Have you had been told by a doctor that you have osteoarthritis at any of these sites", and "Do you experience pain at any of these sites?". The seven anatomical sites were neck, back, hands, shoulders, hips, knees, and feet. Participants were given the choice between answering "yes" or "no". Participants were also asked "Have you been told by a doctor that you have rheumatoid arthritis?" (yes / no). Questions were asked about pain at Phase 1, 2 and 3; doctor diagnosed OA at Phase 1 and 2, and about doctor diagnosed RA at Phase 1.

4.2.4 X-ray

Participants had X-rays of both hips (n=1014) and knees (n=1020) in the standing antero-posterior (AP) position at baseline only. Knee X-rays were taken of both knees with 15° of fixed knee flexion, and pelvic radiographs with both feet in 10° internal rotation. Films were scored individually for osteophytes and joint space narrowing (JSN) on a scale of 0–3 (where 0=no disease and 3=most severe disease) according to the Osteoarthritis Research Society International (OARSI) atlas (Altman, 1995) as previously described (Foley, 2006). Hips and knees with scores 1–3 at any site were classified as having JSN or osteophytes. Two readers simultaneously assessed radiographs with immediate reference to the atlas. Scores for each participant were determined by consensus. Intraobserver repeatability was assessed in 40 participants (intraclass correlation coefficients (ICCs) 0.65 to 0.85 for the knee and 0.60–0.87 for the hip) (Foley, 2006).

4.2.5 Other factors

Leg strength (n=1038) was measured to the nearest kilogram in both legs simultaneously, using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as described in Scott, 2009a (Scott, 2009). This tests isometric strength, predominantly of the quadriceps and hip extensors. Weight was measured to the nearest 0.1 kg (with shoes, socks, bulky clothing and headwear removed) using a single pair of calibrated electronic scales (Seca Delta Model 707). Height was measured to the nearest 0.1 cm (barefoot) using a stadiometer. Body mass index (BMI) was calculated $[\text{weight (kg)} / (\text{height (m)})^2]$. Physical activity levels were determined using pedometers (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) as previously described (Scott, 2009). Briefly, number of steps per day is an average of seven consecutive days and

averaged across two time points in different seasons. We collected self-reported estimates of current cigarette smoking prevalence by questionnaire.

4.2.6 Data analysis

We used Stata 10.0 (StataCorp LP) for statistical analyses. Statistical significance was set as a p value ≤ 0.05 (two-tailed). Sample characteristics were analysed using t-tests and chi-square tests as appropriate. Analyses used total AQoL score as the outcome, and diagnosed OA, JSN, osteophytes and pain as co-predictors. Baseline data was analysed using multiple linear regression. Analyses were first adjusted for age, sex and body mass index (BMI) (Step 1); variables which demonstrated a statistically significant association with total AQoL score were put into the next analysis, with the confounders leg strength and RA. The purpose of this was to determine whether each factor was independently associated with QoL or whether they were no longer significant after adjusting for other factors, suggesting mediation of effect.

Multilevel mixed-effects linear regression were used for longitudinal analyses, clustering on ID, and adjusted for change in BMI and age over time, as these terms were statistically significant. These were intent to treat analyses and used all available data.

We transformed the total AQoL score using a square root transformation in order to meet the residual assumptions underlying linear regression.

Regression coefficients were back-transformed, and the β value was reported for each dependent variable, calculated with all other continuous variables centred at their mean, and dichotomous variables with the reference group having a value of zero. As a sensitivity analysis, we re-ran models in Table 3

without the psychological wellbeing scale to assess the possible effects of psychological distress as an unmeasured confounder of QoL.

4.3 Results

4.3.1 Participants

A total of 1098 people (51% female, mean age 63.0 years) completed baseline questionnaires. Of the 993 participants with complete MRI data at Phase 1 and were therefore invited to return for Phase 2, 875 completed Phase 2 and 768 completed Phase 3. Participants who failed to complete Phase 2 or 3 (including those who did not have baseline MR imaging), were older, had higher BMI and pain at more sites at baseline than those who remained in the study.

4.3.2 Characteristics of the study population at baseline

Table 1 displays the characteristics of the cohort at baseline, stratified by median AQoL score. Those with poorer QoL were older, had higher BMI, walked fewer steps per day, were more likely to be retired or receiving a disability pension and less likely to be employed; and more likely to have no formal educational qualifications (Table 1).

Table 4.1: Characteristics of the study population at baseline, by quality of life[†]

	QoL better than median Mean \pm SEM n (%) n= 525	QoL at median or worse Mean \pm SEM n (%) n= 573	p-value
Age (years)	61.9 \pm 0.3	64 \pm 0.3	<0.001
Gender (% male)	51	47	0.176
BMI weight (cm) / (height (m)) ²	27.3 \pm 0.2	28.4 \pm 0.2	<0.001
Height (cm)	167.7 \pm 0.4	166.3 \pm 0.4	0.006
Weight (kg)	77 \pm 0.6	78.7 \pm 0.6	0.060
Current smokers (%)	12	12	0.782
Number of steps per day	10373.9 \pm 158.3	8597.9 \pm 154.7	<0.001
Education Level			<0.001
No formal qualification	54 (10)	126 (22)	
School or Intermediate certificate	104 (20)	114 (20)	
Higher School or Leaving Certificate	114 (22)	107 (19)	
Trade / apprenticeship	59 (11)	78 (14)	
Certificate / diploma	122 (23)	95 (17)	
University degree or higher	72 (14)	52 (9)	
Current employment			
Employed / self-employed (full or part time)	264 (50)	168 (29)	<0.001
Retired	178 (34)	240 (42)	
Disability pension	4 (0.8)	69 (12)	
Doctor-diagnosed rheumatoid arthritis (%)	6	18	<0.001
Leg strength (kg)	101.6 \pm 1.38	86.3 \pm 1.4	<0.001

[†] QoL was not normal and hence dichotomized at the median.

They also had higher prevalence of diagnosed osteoarthritis (OA) and pain at all sites (Table 4.3).

Health-related QoL scores at baseline were skewed with a mean AQoL score of 7.4 (SD 4.9) and a median of 7.0 (range 0 to 29). Summary results for individual subscales are shown in **Error! Reference source not found..**

Table 4.2: Assessment of Quality of Life (AQoL)[†] subscales at baseline: mean scores and range

	Mean (sd) n=1098	Median	Range
Illness	3.2 (2.6)	3	0 – 9
Independent Living	0.3 (0.9)	0	0 – 7
Relationships	0.7 (1.0)	0	0 – 8
Physical senses	0.9 (1.0)	1	0 – 5
Psychological wellbeing	2.3 (1.6)	2	0 – 9
Total AQoL score	7.4 (4.9)	7	0 – 29

†Higher scores indicate poorer QoL

Distribution was skewed and kurtotic, hence analyses are transformed using a square root transformation, with back transformed results presented

Table 4.3: Osteoarthritis correlates of total AQoL score at baseline, using linear regression

	Prevalence %	Step 1: Multivariable β (95% CI) Adjusted for age, sex and BMI ^f	Step 2: Multivariable β (95% CI) [§] Further adjusted for all variables significant in Step 1
Diagnosed OA of:			
Neck	168 (15)	2.72 (1.80 to 3.64)	-0.32 (-0.96 to 0.32)
Shoulders	193 (18)	3.58 (2.34 to 4.81)	0.23 (-0.64 to 1.10)
Back	167 (15)	3.41 (2.54 to 4.28)	0.71 (0.02 to 1.41)
Hips	97 (9)	3.05 (1.93 to 4.17)	0.04 (-0.74 to 0.82)
Hands	113 (10)	2.32 (1.41 to 3.23)	0.09 (-0.55 to 0.72)
Knees	152 (14)	2.48 (1.52 to 3.43)	0.15 (-0.55 to 0.85)
Feet	103 (9)	3.40 (2.21 to 4.59)	0.30 (-0.49 to 1.09)
Hip JSN (yes / no)	377 (37)	0.34 (-0.31 to 0.99)	–
Knee JSN (yes / no)	688 (67)	0.06 (-0.60 to 0.72)	–
Hip osteophyte (yes / no)	190 (19)	-0.10 (-0.89 to 0.69)	–
Knee osteophyte (yes / no)	143 (14)	-0.31 (-1.21 to 0.59)	–
Pain in the:			
Neck (yes / no)	514 (47)	3.14 (2.58 to 3.71)	0.65 (0.16 to 1.15)
Shoulder (yes / no)	674 (62)	3.35 (2.77 to 3.93)	1.03 (0.52 to 1.54)
Back (yes / no)	481 (44)	2.94 (2.39 to 3.50)	0.58 (0.12 to 1.05)
Hip (yes / no)	481 (44)	2.44 (1.83 to 3.04)	0.26 (-0.18 to 0.70)
Hand (yes / no)	505 (46)	2.63 (2.05 to 3.22)	0.50 (0.04 to 0.96)
Knee (yes/no)	451 (41)	2.72 (2.13 to 3.31)	0.41 (-0.04 to 0.86)
Foot (yes / no)	412 (38)	3.27 (2.64 to 3.89)	1.13 (0.62 to 1.63)

Statistically significant ($p \leq 0.05$) results indicated in bold type

^f after adjustment for age, sex and BMI

[§] further adjusted for diagnosis of RA, arthritis at all sites or pain at all sites and leg strength

[§] R^2 for final model (Step 2)=27%; R^2 excluding pain is 13%; R^2 pain alone=23%.

Diagnosis of RA and leg strength were also associated with QoL, as expected, (Table 4.1), and were adjusted for in final models. Pain at the anatomical regions of interest was common (prevalence 38–62%), with 87% of participants reporting pain in at least one joint. 8% of patients reported pain in all seven regions.

4.3.3 Correlates of quality of life at baseline: cross-sectional analysis

Since presence of pain at the various sites was not strongly collinear, (Pearson's correlation $r = 0.21 - 0.51$), individual sites were entered into the model separately.

Table 4.3 shows that physician diagnosis of OA at any of the sites was associated with poorer QoL after adjustment for age sex and BMI, but only physician diagnosed OA of the back remained significant after further adjustment for RA, diagnosed OA at other sites and pain. Radiographic OA of the hip or knee (JSN, osteophytes) were not associated with QoL in any analysis. Presence or absence of pain at five of the seven sites were independently associated with poor QoL after further adjustment for diagnosis of RA, leg strength, diagnosed OA and pain at other sites. Knee pain was of borderline statistical significance after adjustment for all correlates, $p=0.076$), and hip pain was not significant.

The proportion of variance explained by the final model (R^2 , $n=1017$) was 27%, of which 23% was explained by pain. There was also a strong linear association between the number of sites at which participants reported pain and QoL (Figure 4.1), suggesting a dose-response relationship. This association was significant at all three time points, and relatively constant over time (interaction $p=0.602$).

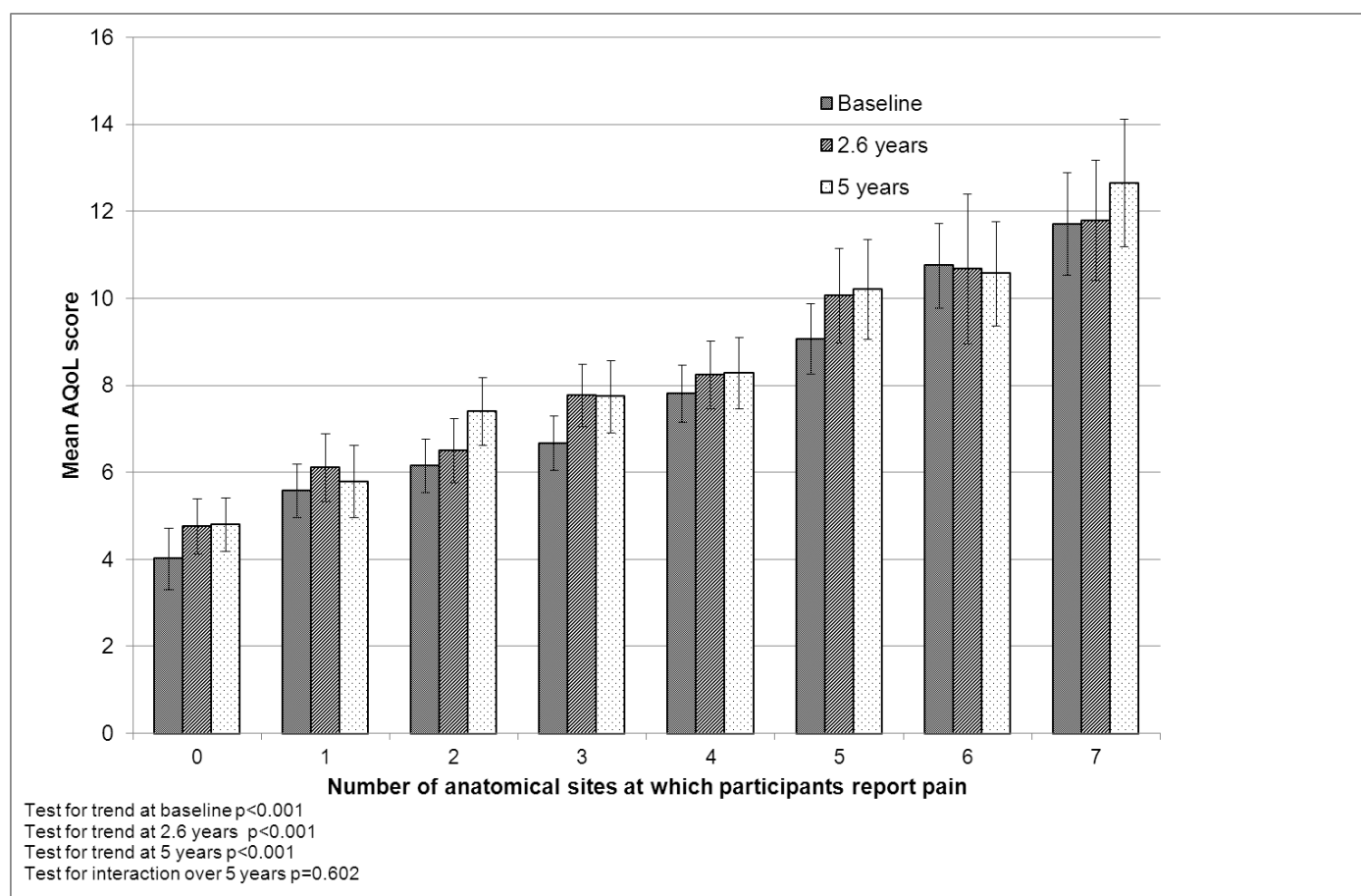


Figure 4.1: Mean total Assessment of Quality of Life (AQL) score over time, by number of sites at which participants report pain and using multilevel mixed-effects linear regression

We conducted sensitivity analyses without the psychological wellbeing subscale in order to assess whether the results from our total AQL score were still valid after removing questions related to psychological factors. The same variables remained significant and coefficients were similar.

4.3.4 Correlates of quality of life over time: Longitudinal analysis

Mean AQoL scores were 7.36 (95% CI 7.07 – 7.65) at Phase 1, 7.53 (95% CI 7.20 – 7.87) at Phase 2 and 7.82 (95% CI 7.47 – 8.17) by Phase 3. Average AQoL scores had significantly worsened by Phase 3 ($p=0.047$), but not Phase 2 (0.44) using unadjusted data and unpaired t-tests. After adjusting for the changing composition of the sample over time using linear mixed models, reduction in means was significant at both Phase 2 and 3 ($p<0.001$).

Table 4.4 shows a similar pattern of correlates of QoL to the analysis of correlates at baseline, although most effect sizes were smaller.

After 2.6 years of observation, diagnosed OA (all sites) and presence or absence of pain (all sites) were significant. After further adjustment for the factors outlined above, diagnosed OA at the back remained significant as did pain at six of the seven anatomical sites. There were no significant interaction terms after adjustment for confounders and other covariates.

After five years of observation, pain at all sites was a significant independent determinant of QoL (Table 4.4). QoL amongst participants with neck pain remained stable whilst steadily worsening in those with no neck pain ($p=0.02$ for interaction) but all other tests for interaction were not significant.

Table 4.4: Longitudinal analysis of arthritis correlates of total AQoL score over five years of follow up, using multilevel mixed-effects modelling

	Baseline to Phase 2 (2.6 year follow up)		Baseline to Phase 3 (5 year follow up)	
	Step 1: Multivariable β (adj. age sex BMI, change in BMI and age over time)	Step 2: Multivariable β Adjusted further [‡]	Step 1: Multivariable β (adj. age sex BMI, change in BMI and age over time)	Step 2: Multivariable β Adjusted further [‡]
Diagnosed OA of:				
Neck	1.55 (0.96 to 2.15)	0.01 (-0.5 to 0.52)		
Shoulders	1.92 (1.22 to 2.61)	0.37 (-0.23 to 0.96)		
Back	1.76 (1.23 to 2.28)	0.59 (0.12 to 1.06)		
Hips	1.19 (0.54 to 1.84)	-0.20 (-0.73 to 0.32)		
Hands	1.35 (0.79 to 1.90)	0.19 (-0.28 to 0.66)		
Knees	1.50 (0.91 to 2.08)	0.15 (-0.34 to 0.64)		
Feet	1.40 (0.72 to 2.09)	0.12 (-0.44 to 0.68)		
Presence or absence of pain in the:				
Neck	1.79 (1.4 to 2.18)	0.55 (0.19 to 0.91)	1.20 (0.89 to 1.51)	0.42 (0.14 to 0.71)
Shoulders	1.80 (1.42 to 2.18)	0.66 (0.31 to 1.00)	1.36 (1.06 to 1.66)	0.64 (0.36 to 0.91)
Back	1.82 (1.45 to 2.19)	0.67 (0.33 to 1.00)	1.39 (1.09 to 1.68)	0.66 (0.39 to 0.94)
Hips	1.46 (1.07 to 1.85)	0.52 (0.19 to 0.85)	1.16 (0.85 to 1.47)	0.47 (0.20 to 0.74)
Hands	1.20 (0.82 to 1.59)	0.19 (-0.13 to 0.51)	0.91 (0.60 to 1.22)	0.27 (0.01 to 0.53)
Knees	1.51 (1.12 to 1.90)	0.43 (0.10 to 0.75)	1.10 (0.79 to 1.41)	0.44 (0.17 to 0.70)
Feet	0.98 (0.65 to 1.32)	0.36 (0.09 to 0.62)	0.75 (0.47 to 1.02)	0.26 (0.03 to 0.49)

Statistically significant ($p \leq 0.05$) results indicated in bold type

[‡] Results further adjusted for diagnosed OA at all sites, pain at all sites, presence of rheumatoid arthritis and leg strength

[‡] Results further adjusted as for the analyses for Baseline to Phase 2, but without Diagnosed OA as this was not asked at Phase 3.

5 year follow up data includes data collected at Phase 1, 2 and 3 and is not limited to participants with complete data.

Radiographs not included as they were only collected at Phase 1.

4.4 Discussion

This population-based prospective study describes the contribution of multiple osteoarthritic correlates of QoL over five years of observation.

Physician diagnosed OA of the back and pain at all sites were independent and stable correlates of QoL, and pain at multiple sites has an additive deleterious effect on QoL. With the exception of the back, pain appeared to mediate the association between diagnosed OA and QoL. Radiographic osteoarthritis was not associated with QoL.

In this study, the strongest musculoskeletal correlate of QoL was pain. Pain is a priority for patients seeking care (Heiberg and Kvien, 2002) and thus it is perhaps not surprising that pain largely mediated the association between doctor diagnosed OA and QoL. Further, pain assessed at one site in cross sectional studies is known to be associated with poorer QoL (Hill, 2008; Rezai, 2009), but no studies that have looked at pain at many sites. Our data suggests that pain at all sites measured independently contribute to QoL, there is a dose response association between number of pain sites and QoL, and severity of pain is also related to QoL. Our data suggests that pain is very common in older adults in the community. Given that pain at individual joints and overall number of sites of joint pain were associated with poor QoL, this suggests that interventions to reduce the frequency and intensity of pain may be effective in improving QoL at the population level.

While there are some inconsistencies in the three analyses, the most weight should be put on the analysis over five years as it uses all the data and therefore is the most powerful. These results confirm and extend the findings of Woo et al (2009), where pain at the back, hip (men only) and knees was

associated with QoL over time in ethnic Chinese. Pain in the shoulders and back were the most important factors in our analyses, but knees, hips and even hands and feet were significant. The inconsistency with the hip may, in part, be due to patients have difficulty locating the correct anatomical position of the hips (Birrell, 2005), or that pain in the knee can actually be referred from the hip (Zhai, 2006). Knee pain was of borderline significance in cross-sectional analyses but became significant over time.

Diagnosed OA of the back was also an independent correlate of poor QoL (both in cross-sectional and longitudinal analyses), but diagnosed OA of the neck, shoulders, hips, hands, knees and feet were not once adjustment was made for the multiple sites of OA and for pain. This suggests that while pain mediates the associations between diagnosed OA and QoL at sites other than the back (neck, shoulders, hands, hips, knees and feet), the association between diagnosed OA of the back and QoL is only partially mediated by pain. It is well known that psychological factors such as depression are associated with chronic back pain but unfortunately we were not able to assess these in the current study.

There was no association between radiographic osteoarthritis and QoL at baseline, after adjusting for age, sex and BMI. This suggests that radiographic findings make no independent contribution to QoL, consistent with other studies which showed that the association between radiographic OA of the hand and function was largely mediated by pain (Jones, 2001), and that pain is a better predictor of disability than radiographic change (Creamer, 2000; Guccione, 1990; Jordan, 1997). This differs from the findings of other studies (Norimatsu, 2011; Muraki, 2011), who found that radiographic OA was associated cross-sectionally with different disease-specific measure of

QoL, after adjustment for pain and other covariates. Both of these measures of QoL had pain as a subscale, so this may explain why they found an association yet we did not. A strength of our study is that, unlike Norimatsu and colleagues, we have collected (self-reported) diagnosis of OA and radiographic findings separately (in addition to pain), and while finding them to be correlated, when both diagnosis and radiography appear together in one model, radiographic findings are no longer associated with QoL. Our data demonstrates that diagnosis of OA reflects more than radiographic evidence of joint damage, but that with the exception of diagnosed OA of the back, is not independent of pain.

Strengths of this study include the random population-based sampling and comprehensive data collection, and five-year period of observation, providing excellent external validity for our findings. Limitations include absence of information on psychological factors, such as diagnosed mental health conditions or psychological distress: this limits our ability to consider such conditions as covariates or effect modifiers, but our model is robust whether or not the mental health component of QoL is included, suggesting this is not a major issue. Additionally, the initial response rate of 57%, while lower than desirable, is similar to other comparable Australian studies (Hill, 2008), and a lower response rate does not mean that relationships between outcome and exposure are necessarily biased (Carter, 2012). Participants who did not continue in the study were older, heavier, with pain at more sites at baseline than the remaining participants. This should reduce the observed effect size of our findings, but since few associations were of borderline significance this should not have altered our conclusions. We did not seek to confirm doctor-diagnosed cases of arthritis, and therefore participants may have under-or

over-reported diagnosed arthritis, and the extent to which this may have affected the findings of the study is unclear. However, use of self-reported doctor diagnosed OA appears to be a reasonable proxy for OA, as JSN was more common in participants reporting doctor-diagnosed OA at the hips and knees (hips OR 2.3, $p < 0.001$; knees OR 1.6, $p = 0.023$), and osteophytes more common in participants reporting knee (OR 4.10, $p < 0.001$), but not hip OA (OR 0.94, $p = 0.83$). We had X-rays only of the hips and knees, and so are not able to assess the association between ROA and QoL at other anatomic sites. However, unless the causal pathways at other sites are substantially different to those at the knees and hips, it is unlikely that radiographic OA at these sites would add any new information to the models.

In conclusion, pain is the strongest musculoskeletal correlate of QoL, which has an additive deleterious effect on QoL, and mediates the effect of diagnosed OA (except in OA of the back). These associations are stable over time suggesting that pain has a consistent rather than an increasing deleterious effect. Since we found that the same factors were associated with quality of life over time as in the baseline analysis, this suggests that quality of life tracks over a five year period.

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Chapter 5

Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a 5-year longitudinal study.

Published in:

<http://www.ncbi.nlm.nih.gov/pubmed/23595144>

Laslett LL, Quinn SJ, Burgess JR, Parameswaran V, Winzenberg TM, Jones G, Ding C. .2013, Moderate vitamin D deficiency is associated with changes in knee and hip pain in older adults: a five year longitudinal study. *Ann Rheum Dis.* 2013 [epub before print].

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Chapter 6

Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial.

Published In:

<http://www.ncbi.nlm.nih.gov/pubmed/22863612>

doi: 10.1016/j.joca.2012.07.019

Laslett LL, Quinn S, Darian-Smith E, Kwok M, Fedorova T, Körner H, Steels E, March L, Jones G. 2012, Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial. *Osteoarthritis Cartilage*. 2012;20(11):1209-16.

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copyright or proprietary reasons.

Chapter 7

Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial.

Published In:

<http://www.ncbi.nlm.nih.gov/pubmed/22355040>

doi: 10.1136/annrheumdis-2011-200970.

Laslett LL, Doré DA, Quinn SJ, Boon P, Ryan E, Winzenberg TM, Jones G. 2012, Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis.* 2012 Feb 21;71(8):1322-8.

Chapter 8: Summary and future directions

Chapter 8. Summary and future directions

8.1 Introduction

As has been described in this thesis, arthritis is the most common cause of chronic pain in older people (Peat, 2001; Britt, 2010), affecting an estimated 31% of Australians (AIHW, 2010), and is expensive, constituting the fourth largest component of direct health expenditure in 2004–05, at AUD\$4.0 billion (AIHW, 2009). Increases in expenditure are predicted to continue, and to increase by a factor of 2 by 2032–33 (Goss, 2008), driven by the ageing population the volume of treatment(s) for each person. Pain is an important clinical symptom, predicting clinically relevant outcomes including disability (Croft, 2005) and joint replacement (Gossec, 2005; Hawker, 2006; Conaghan, 2010; Jüni, 2003), and is a priority for patients (Heiberg and Kvien, 2002).

Despite the large disease burden, there are no proven preventative strategies, but there have been a few clinical trials in addition to the work presented in this thesis (Bruyere, 2008; Esenyel, 2012; Reginster, 2012), all using agents with well-described effects in bone. None have demonstrated change in structural endpoints in addition to pain. Conventional treatment of OA remains mostly palliative and expensive and there is considerable scope for improvements in treatments, both in terms of treatments which modify structure and pain, and safe treatments which confer additional pain benefits.

8.2 Future directions

8.2.1 Musculoskeletal pain and quality of life

Investigations on the impact of musculoskeletal pain and radiographic OA on health related QoL in older adults living in the community are presented in Chapter 4. We concluded that radiographic findings (JSN, osteophytes)

make no independent contribution to QoL, and that pain tracks over time.

This supports a focus on pain-relieving interventions, and that reducing pain could change the trajectory of quality of life in the medium term. Agents that slow structural progression of osteoarthritis are extremely important, but such agents must also improve pain if they are to improve the quality of people's lives.

8.2.2 Serum 25–OHD and change in knee and hip pain over time

Investigations on associations between serum 25–OHD and change in knee pain over 5 years and change in hip pain over 2.6 years are presented in Chapter 5. We found that there was no linear association between serum 25–OHD and change in knee or hip pain using the original values of 25–OHD, but that having serum 25–OHD below 25 nmol/L (moderately deficient) was a novel determinant of musculoskeletal pain. Mild vitamin D deficiency is endemic in Tasmanian adults (van der Mei, 2012), as it is elsewhere in the world but moderate deficiency is uncommon in most populations. This study suggests that supplementation may help pain in this small subgroup but this needs to be tested in randomised trials before supplementation can be recommended, or guidelines developed for the use of supplements. A randomised controlled trial of the effects of vitamin D in OA is underway at our centre (the Vitamin D Effects on OA, or VIDEO study (Cao, 2012)), in which vitamin D supplementation (50,000 IU compounded vitamin D3 capsule monthly) or identical inert placebo is issued monthly to participants with symptomatic knee OA and serum 25–OHD of 12.5 – 60 nmol/L for two years. Outcomes from the VIDEO study will include the effect of vitamin D3 supplementation on pain, as measured by the WOMAC pain score.

Therefore, the VIDEO study will be able to determine whether vitamin D

supplementation is effective in improving knee pain in persons with clinical knee osteoarthritis, and whether this effect is observed only in persons with baseline 25–OHD levels of 25–30 nmol/L or whether such benefits apply to all study patients (12.5 to 60 nmol/L).

Two recent trials have demonstrated increased risk of fractures (Sanders, 2010; Smith, 2007) and falls (Sanders, 2010) using large (300,000IU) annual intramuscular doses of vitamin D2 or vitamin D3. This has overturned the previous view attained from studies with more frequent dosing regimes that vitamin D supplementation was safe as long as 25–OHD levels remained below the toxic levels of 275–500 nmol/L (Jones, 2008). The results of these trials are a cautionary tale of the importance of randomised trials in determining efficacy and safety before treatments are introduced into clinical practise.

8.2.3 4Jointz trial

A randomised controlled trial of 4Jointz vs placebo was conducted (see Chapter 6). We demonstrated that topical treatment using 4Jointz is a safe and effective treatment for the symptoms of knee OA in participants with clinical OA and moderate knee pain on most days. In particular, use of 4Jointz reduced pain and increased muscle strength, but had no effect on systemic inflammation or cartilage breakdown over 12 weeks of treatment. This was particularly notable as these benefits were in addition to the effect of other treatments.

We observed higher dropout rates in the group receiving 4Jointz, partially attributable to rashes (localised skin irritation at the site of application). This highlights the importance of conducting clinical trials on all medications, as rashes were not reported as an adverse event in previous studies using

topical preparations of comfrey. It is possible that rashes were related to the other components of 4Jointz, such as tannic acid. The pharmaceutical company may consider how they can make the preparations less irritating in order to minimise rashes.

Since post-hoc analyses suggested that treatment may be most effective in women and those with milder radiographic OA, future studies should consider including these populations, and for longer duration than 12 weeks.

This trial also suggests the value of using add-on trials in OA, where a medication is given to patients in addition to their other medications.

8.2.4 ZAP trial

This trial investigated the effect of a single dose of zoledronic acid (5mg) on persons with moderately severe knee pain, clinical knee OA and BMLs (see Chapter 7). Use of ZA significantly reduced VAS pain scores, areal size of BMLs after 6 months, and proportion with improvement in BML size. This is the first occasion that any osteoarthritic treatment has demonstrated structural modification of BMLs (or indeed any other structure); therefore this observation is completely novel. Previous investigations of potential structure-modifying drugs did not live up to expectations (Bingham, 2006; Raynauld, 2008). For ZA to be truly disease modifying, evidence of change in cartilage endpoints or joint replacement will be required. To this end, our research group have been successful in obtaining a National Health and Medical Research Council Project Grant (2012 Application ID 1045415). This will fund a two year randomised controlled trial of yearly infusion of ZA (5mg) on cartilage volume, along with other endpoints collected in the shorter trial presented as part of this thesis (BMLs, pain, function) as well as cartilage markers and joint replacement.

One of the observations from the ZAP trial was that 39% of participants receiving ZA improved, whereas only 18% receiving placebo improved, representing an odds ratio of 5.0 ($p=0.044$). This is a significant difference, showing that ZA is effective in reducing the size of BMLs, with large enough reductions that we expected to observe a clinically significant reduction in pain. However, even in the group who received ZA, 61% had an increase in their BMLs or no change (compared to 82% in the placebo group). Clearly some patients are responding to treatment whereas others are not. Since the pathology of BMLs are heterogeneous (Zanetti, 2000; Taljanovic, 2008), one of the explanations for this is that some histological profiles respond to osteoclast-mediated ZA therapy whereas others do not. Unfortunately, no markers are yet available for typing of BMLs using non-invasive methods, as biopsies are not feasible in this population. Similarly, some participants had evidence of reduction in the size of BMLs but not reduction in pain, which we attribute to presence of other pathologies which cause pain, such as joint effusions. In the new, NHMRC-funded two-year RCT with cartilage endpoints which will begin in 2013, we plan to investigate the effect of other pathology and disease characteristics on response to ZA.

This clinical trial also provides evidence of a “bone-specific” phenotype of OA (Walsh and Chapman, 2011) which is highly likely to be responsive to treatment with bisphosphonates.

8.2.5 Challenges in clinical trials in osteoarthritis

8.2.5.1 Choice of study patients

Animal models suggest that synovitis and BMLs are very early signs of OA, preceding cartilage erosion and degeneration (Libicher, 2005); thus these may be optimal markers to target in achieving disease modification, as they

occur early in the disease course when less damage has occurred. Yet typical patients in knee OA trials with structural endpoints are patients with much later stages of OA, ie Kellgren and Lawrence grade 2 and 3. Intervening earlier in the disease course is always preferable, but additionally choosing patients with radiographic OA for interventional studies has additional problems, as the presence of radiographic OA predicts patients who lose cartilage faster (Mazzuca, 2005; Saunders, 2011), and this has implications for participant selection in clinical trials as the outcomes of treating these different Oa phenotypes may have different outcomes. This suggests that selection of study patients is crucial when planning intervention studies, and in evaluating their results.

8.2.5.2 Choice of outcome measures

Change in joint space width (JSW) at the tibiofemoral joint is currently the gold standard for assessing osteoarthritis disease modification in clinical trials, (Conaghan, 2011) and is mandated by the Food and Drug Administration and European Medications Agency as a proxy endpoint to determine efficacy of disease modifying osteoarthritis drugs. In cross-sectional studies, the amount of cartilage volume assessed by magnetic resonance imaging (MRI) and JSW as assessed by radiograph are strongly correlated. However, JSW is also associated with meniscal pathology (Berthiaume, 2005; Adams, 1999) and cartilage defects, (Ding, 2005) suggesting that multiple abnormalities contribute to narrowing of joint space width (JSW). There is limited longitudinal data; however data from our centre demonstrates that both change in cartilage volume and meniscal extrusions modestly predict change in joint space width; however, over 90% of the variation in change in joint space remains unexplained (Hall, 2012).

Using MR imaging in preference to radiographs should be a better outcome measure as it enables direct (vs indirect) visualisation of these structures, and has been validated in cadaveric studies, (Cicuttini, 1999) and predicts clinical outcomes such as joint replacement (Cicuttini, 2004). Overall, cartilage loss seen on MRI is more sensitive than X-ray change as an outcome measure.

There are other issues in using radiographs as outcomes. Structures seen on radiographs may not be direct sources of pain, and therefore are of limited value in assessing factors causing pain. Also, the changes in JSW in some trials (even large trials) have shown mean changes that were less than the measurement error of the technique of evaluation}, despite large numbers of patients and state of the art protocols. (Brandt, 2005; Bingham, 2006)

Despite these shortcomings, MR imaging is yet to replace radiographs as routine an outcome measures in studies investigating structural outcomes.

8.2.5.3 *Subtypes or phenotypes of osteoarthritis*

Osteoarthritis can result from an extremely diverse range of pathologies and pathological processes, resulting in a heterogeneous mix of pathological processes and tissue subtypes amongst patients diagnosed with OA. This creates a challenge for clinical trials in that a treatment applied to a particular study group may only be effective in a small subset of that group. Therefore, separating study populations into subgroups with particular features that are likely to respond (or not respond) to particular treatments have advantages (Lane, 1999). One such phenotype is a “bone-specific phenotype” (Walsh and Chapman, 2011) in patients with BMLs. Bone marrow lesions identify regions of increased subchondral bone turnover and therefore may provide a biomarker that can predict response to

bisphosphonates. Phenotypes postulated by other authors are post-traumatic (acute or repetitive), metabolic, ageing, genetic and pain (Bijlsma, 2011), and rate of progression or prognosis (Lane, 1999); each with different aetiological features, causal pathways, affected sites and effective treatments. Identifying subtypes or phenotypes of OA is likely to assist in targeting treatment to patients who are the most likely to benefit.

8.2.6 Conclusions

In conclusion, this analysis of data from a prospective population-based cohort study and two randomised controlled trials demonstrate that pain is an independent correlate of quality of life, that one of the determinants of knee (and possibly hip) pain over time is moderate vitamin D deficiency, and that treatment of patients with clinical knee OA and pain on most days with either ZA infusion or application of 4Jointz reduces knee pain. Most importantly, we have demonstrated that ZA may be a disease-modifying OA drug which reduces the size of BMLs in addition to reducing pain. Future work is underway on larger multicentre clinical trials.

Appendix 1: Questionnaires

Appendix 1 Questionnaires

A1.1 The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and questions on diagnosed OA and joint pain

5056469678

5 Rate the following today

This section assesses pain, stiffness and functional deficit on a scale from 1 - 10

Example

Example of no pain none 1 2 3 4 5 6 7 8 9 10 severe

Example of severe pain 1 2 3 4 5 6 7 8 9 10 severe

1. Referring to your knees only how much pain do you experience when

- | | none | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | severe |
|------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| a. Walking on a flat surface | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| b. Going up and down stairs | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| c. At night while in bed | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| d. Sitting or lying | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| e. Standing upright | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Referring to your knees only how much stiffness do you experience

- | | none | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | severe |
|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| a. After first awakening | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| b. Later in the day | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

3. Referring to your knees only how much functional deficit do you experience when

- | | none | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | severe |
|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| a. Descending stairs | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| b. Ascending stairs | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| c. Rising from bed | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| d. Rising from sitting | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| e. Putting on socks | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| f. Taking off socks | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| g. Bending to the floor | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| h. Lying in bed | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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Question 3 continued

none

severe

- i. Walking on flat surface ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- j. Getting in/out of the bath ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- k. Standing ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- l. Sitting ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- m. Getting in/out of the car ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- n. Getting on/off the toilet ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- o. Heavy domestic chores ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- p. Light domestic chores ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
- q. Shopping ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

4. Do you have pain at any of these sites?

- a. Neck Yes ☐ 1 No ☐ 2
- b. Back Yes ☐ 1 No ☐ 2
- c. Hands Yes ☐ 1 No ☐ 2
- d. Shoulders Yes ☐ 1 No ☐ 2
- e. Hips Yes ☐ 1 No ☐ 2
- f. Knees Yes ☐ 1 No ☐ 2
- g. Feet Yes ☐ 1 No ☐ 2

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5. Have you been diagnosed by a Doctor with Osteoarthritis at any of the following sites?

- | | | | | |
|--------------|-----|-------------------------|----|-------------------------|
| a. Neck | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| b. Back | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| c. Hands | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| d. Shoulders | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| e. Hips | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| f. Knees | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |
| g. Feet | Yes | <input type="radio"/> 1 | No | <input type="radio"/> 2 |

Comments

A1.2 Smoking questions

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6 Smoking Questions

The following questions relate to smoking

NOTE : A "regular smoker" is someone who has smoked at least 7 cigarettes, cigars or pipes every week for at least 3 months

1. Have you ever been a "regular smoker"? Yes ☐ ₁ No ☐ ₂

If "NO" go to the next section of this questionnaire.

2. At what age did you first become a "regular smoker"?

Years Months

3. Are you currently a "regular smoker"? Yes ☐ ₁ No ☐ ₂

If "YES" go to question 5

4. How old were you when you last gave up being a "regular smoker"? Years of Age

5. Have there been any times of at least 6 months or more when you stopped smoking "regularly" but then smoked again afterwards?

Yes ☐ ₁ No ☐ ₂

If "YES" please indicate how old you were and for how long you stopped.

If this happened more than once record each time.

	Age	Period of time you did not smoke	
		Years	Months
Example	<input type="text"/> 2 <input type="text"/> 5	<input type="text"/> 1	<input type="text"/> 9
1st time	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
2nd time	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
3rd time	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
4th time	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
5th time	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>

6. How many cigarettes, pipes or cigars DO/DID you smoke daily on week days?

- | | |
|------------|-------------------------|
| 1 - 5 | <input type="radio"/> 1 |
| 6 - 15 | <input type="radio"/> 2 |
| 16 - 25 | <input type="radio"/> 3 |
| 26 - 35 | <input type="radio"/> 4 |
| 36 - 45 | <input type="radio"/> 5 |
| 46 or more | <input type="radio"/> 6 |

7. How many cigarettes, pipes or cigars DO/DID you smoke daily on weekends?

- | | |
|------------|-------------------------|
| 1 - 5 | <input type="radio"/> 1 |
| 6 - 15 | <input type="radio"/> 2 |
| 16 - 25 | <input type="radio"/> 3 |
| 26 - 35 | <input type="radio"/> 4 |
| 36 - 45 | <input type="radio"/> 5 |
| 46 or more | <input type="radio"/> 6 |

8. What type of tobacco DO/DID you usually smoke?

- | | |
|----------------------------|-------------------------|
| Cigarettes - tailor made | <input type="radio"/> 1 |
| Cigarettes - roll your own | <input type="radio"/> 2 |
| Pipes | <input type="radio"/> 3 |
| Cigars | <input type="radio"/> 4 |

A1.3 Assessment of quality of life (AQoL)**ID** _____**Assessment of Quality of Life (AQOL)****INSTRUCTIONS:**

Please circle the alternative that best describes you during the last week.

ILLNESS

1. Concerning my use of prescribed medicines:

- A. I do not or rarely use any medicines at all.
- B. I use one or two medicinal drugs regularly.
- C. I need to use three or four medicinal drugs regularly.
- D. I use five or more medicinal drugs regularly.

2. To what extent do I rely on medicines or a medical aid? (NOT glasses or a hearing aid.) (For example: walking frame, wheelchair, prosthesis etc.)

- A. I do not use any medicines and/or medical aids.
- B. I occasionally use medicines and/or medical aids.
- C. I regularly use medicines and/or medical aids.
- D. I have to constantly take medicines or use a medical aid.

3. Do I need regular medical treatment from a doctor or other health professional?

- A. I do not need regular medical treatment.
- B. Although I have some regular medical treatment, I am not dependent on this.
- C. I am dependent on having regular medical treatment.
- D. My life is dependent upon regular medical treatment.

INDEPENDENT LIVING

4. Do I need any help looking after myself?

- A. I need no help at all
- B. Occasionally I need some help with personal care tasks.
- C. I need help with the more difficult personal care tasks.
- D. I need daily help with most or all personal care tasks.

5. When doing household tasks: (For example, preparing food, gardening, using the video recorder, radio, telephone or washing the car)

- A. I need no help at all.
- B. Occasionally I need some help with household tasks.
- C. I need help with the more difficult household tasks.
- D. I need daily help with most or all household tasks.

6. Thinking about how easily I can get around my home and community:

- A. I get around my home and community by myself without any difficulty.
- B. I find it difficult to get around my home and community by myself.
- C. I cannot get around the community by myself, but I can get around my home with some difficulty.
- D. I cannot get around either the community or my home by myself.

SOCIAL RELATIONSHIPS

7. Because of my health, my relationships (for example: with my friends, partner or parents) generally:

- A. Are very close and warm.
- B. Are sometimes close and warm.
- C. Are seldom close and warm.
- D. I have no close and warm relationships.

8. Thinking about my relationship with other people:

- A. I have plenty of friends, and am never lonely.
- B. Although I have friends, I am occasionally lonely.
- C. I have some friends, but am often lonely for company.
- D. I am socially isolated and feel lonely.

9. Thinking about my health and my relationship with my family:

- A. My role in the family is unaffected by my health.
- B. There are some parts of my family role I cannot carry out.
- C. There are many parts of my family role I cannot carry out.
- D. I cannot carry out any part of my family role.

PHYSICAL SENSES

10. Thinking about my vision, including when using my glasses or contact lenses if needed:

- A. I see normally.
- B. I have some difficulty focusing on things, or I do not see them sharply.
For example: small print, a newspaper, or seeing objects in the distance.
- C. I have a lot of difficulty seeing things. My vision is blurred.
For example: I can see just enough to get by with.
- D. I only see general shapes, or am blind. For example: I need a guide to move around.

11. Thinking about my hearing, including using my hearing aid if needed:

- A. I hear normally.
- B. I have some difficulty hearing or I do not hear clearly.
For example: I ask people to speak up, or turn up the TV or radio volume.
- C. I have difficulty hearing things clearly. For example: Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.
- D. I hear very little indeed. For example: I cannot fully understand loud voices speaking directly to me.

12. When I communicate with others: (For example: by talking, listening, writing or signing)

- A. I have no trouble speaking to them or understanding what they are saying.
- B. I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.
- C. I am only understood by people who know me well. I have great trouble understanding what others are saying to me.
- D. I cannot adequately communicate with others.

PSYCHOLOGICAL WELLBEING

13.If I think about how I sleep:

- A.I am able to sleep without difficulty most of the time.
- B.My sleep is interrupted some of the time, but I am usually able to go back to sleep without difficulty.
- C.My sleep is interrupted most nights, but I am usually able to go back to sleep without difficulty.
- D.I sleep in short bursts only. I am awake most of the night.

14.Thinking about how I generally feel:

- A.I do not feel anxious, worried or depressed.
- B.I am slightly anxious, worried or depressed.
- C.I feel moderately anxious, worried or depressed.
- D.I am extremely anxious, worried or depressed.

15.How much pain or discomfort do I experience?

- A.None at all.
- B.I have moderate pain.
- C.I suffer from severe pain.
- D.I suffer unbearable pain.

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A1.4 Knee Injury and Osteoarthritis Scale

Arthritis relief Plus - KOOS KNEE SURVEY

Date: / / Patient ID:

Name:

Site Number:

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S3. Does your knee catch or hang up when moving?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S4. Can you straighten your knee fully?

Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

S5. Can you bend your knee fully?

Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

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Arthritis Relief Plus KOOS

Page 1

P1. How often do you experience knee pain?

Never Monthly Weekly Daily Always
☐ ☐ ☐ ☐ ☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P3. Straightening knee fully

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P4. Bending knee fully

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P5. Walking on flat surface

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P6. Going up or down stairs

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P7. At night while in bed

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P8. Sitting or lying

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

P9. Standing upright

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

A2. Ascending stairs

None Mild Moderate Severe Extreme
☐ ☐ ☐ ☐ ☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A4. Standing

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A14. Sitting

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Appendix 1: Knee Injury and Osteoarthritis Scale

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SP2. Running

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Thank you very much for completing all the questions in this questionnaire.

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Appendix 2

Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study.

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Laslett LL, Just (nee Foley) SJ, Quinn SJ, Winzenberg TM, Jones G. 2012, Excess body fat is associated with higher risk of vertebral deformities in older women but not in men: a cross-sectional study. *Osteoporos Int.* 2012;23:67-74.

Appendix 3: Report on 4Jointz trial prepared for the pharmaceutical company

Appendix 3 A 12 week randomised controlled trial of 4Jointz for symptomatic knee osteoarthritis

Report prepared for Arthritis Relief Plus Ltd

February 2012

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List of abbreviations

ACR	American College of Rheumatology
BMI	Body Mass Index
CTX-2	C-terminal cross linking telopeptide of type II collagen: a marker of cartilage tissue degradation.
eGFR	Estimated glomerular filtration rate: a measure of kidney function.
ITT	Intent to treat: an approach to data analysis.
JSN	Joint space narrowing: the space between tibia and femur, as seen on radiographs.
KOOS	Knee Injury and Osteoarthritis Outcome Score
IL-6	Interleukin-6, a marker of inflammation
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
VAS	Visual analog score: a tool for measuring pain intensity.

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Abstract

Objective: To assess the efficacy of thrice daily topical 4Jointz utilizing Acteev technology (a novel and patented combination of a standardized comfrey extract and a pharmaceutical grade tannic acid, 3.5 g/day), or placebo on osteoarthritic knee pain, markers of inflammation and cartilage breakdown over twelve weeks in a double-blind randomised controlled trial.

Patients and methods: Adults aged 50-80 years (n=133) with clinical knee osteoarthritis (OA) according to the ACR criteria were randomised to receive either 4Jointz or placebo in addition to existing medications. Pain and knee function were measured using a visual analogue scale (VAS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scale at baseline, 4, 8 and 12 weeks. Inflammation was measured using IL-6 and cartilage breakdown measured using CTX-2, at baseline and twelve weeks.

Results: Pain scores were significantly reduced in the group who received 4Jointz compared to the group who received placebo after twelve weeks using both the VAS (-9.9mm, $p=0.034$) and the KOOS pain scale (5.7, $p=0.047$). This effect decreased markedly within 4 weeks of cessation of treatment. In addition, muscle strength improved compared to placebo (+2.9 kg, $p=0.02$) after twelve weeks. Changes in IL-6 and CTX-2 were not significant (+0.1, $p=0.98$; -23.0, $p=0.44$). Reduction in paracetamol daily dose in patients using paracetamol at baseline was clinically (but not statistically) significant by twelve weeks (-404 mg, $p=0.35$). Post hoc analyses suggested that the treatment may be most effective in women (VAS -16.8mm, $p=0.008$) and those with milder radiographic osteoarthritis (VAS -16.1mm, $p=0.009$). Local rash was more common amongst participants

receiving 4Jointz (21% v 1.6%, IRR 13.2, $p=0.013$), but only 26% ($n=4$) of participants with rashes discontinued treatment. There were no changes in systemic blood results and no differences in adverse events between patients receiving 4Jointz and placebo.

Conclusions: Topical treatment using 4Jointz reduced pain and increased muscle strength but had no effect on inflammation or cartilage breakdown over twelve weeks of treatment.

A3.1 Introduction

Knee osteoarthritis (OA) is common and is associated with pain and ongoing disability. Management of osteoarthritis involves symptom control, usually non-steroidal anti-inflammatory medications (NSAIDs) or analgesic medication in early arthritis, and then joint replacement when the disease progresses to more severe stages.

The controversy surrounding the use of the COX-2 inhibitor class of NSAIDs and heightened cardiovascular risk (Bombardier, 2000; Bresalier, 2005; Caughey, 2011; Solomon, 2005), highlights the importance of finding safer treatment options to minimise adverse side effects. Natural agents such as capsaicin (Katz and Shah, 2009) and vitamins (McAlindon, 1996) have demonstrated improved overall patient outcomes, and may play a role in treatment of OA even if they are only moderately effective.

Comfrey (*Symphytum officinale*) is traditionally used for the treatment of bone fractures, sprains and wounds (Bleakley, 2008), as it demonstrates anti-inflammatory and analgesic properties. A topical comfrey application (vs. placebo) on acute ankle sprains in 142 participants has been shown to decrease pain and swelling and improve mobility (Koll, 2004). In other studies on ankle distortions sole comfrey therapy was reported as being as effective and possibly superior to diclofenac gel (D'Anchise, 2007; Predel, 2005). Comfrey has also been used in an earlier study to specifically treat OA with two thirds of recipients reducing or discontinuing their NSAID treatment (Koll and Klingenburg, 2002). Moreover, in a study involving 220 patients diagnosed with OA, those utilising topical Comfrey therapy reported a marked reduction in VAS pain scores (Grube, 2007).

Persons with OA have been reported to have high levels of free radicals and reduced levels of antioxidants within the joint fluid (Regan, 2008). The presence of oxygen free radicals in the synovial joint fluid of persons with osteoarthritis act as chemical messengers responsible for the pathogenesis of osteoarthritis (Yudoh, 2005). Antioxidants (such as tannic acid) are protective against the extracellular matrix cartilage degradation that radicals yield (Cho, 2009) and can also augment glycosaminoglycan binding to collagen. This ultimately contributes to the structural reinforcement of synovial articulating surfaces (Levanon and Stein, 1995). Preparations of tannic acid have been found to be superior to placebo in reducing pain and stiffness and improving physical function in primary OA (McAlindon, 1996). Therefore, a number of complementary medicinal agents may be effective in reducing pain and inflammation. A pilot study of treatment using two different concentrations of comfrey vs placebo (Smith and Jacobson, 2011) showed that the comfrey / tannic acid mixtures were both superior to placebo in reducing WOMAC pain and stiffness scores. In a previous study, (Grube, 2007) researchers compared a comfrey root extract with placebo for painful knee OA and observed a 40mm difference in pain VAS score, and 46mm reduction in WOMAC score between comfrey and placebo after three weeks. However, this trial has substantial methodological weaknesses which reduce confidence in its' findings. These include: short duration of follow up; absence of baseline patient summary data; lack of information on how participants were randomised, how blinding was achieved for patients or assessors, or methods used to confirm knee OA.

This study compared the effect of thrice daily topical 4Jointz utilizing Acteev technology (a novel and patented combination of a standardized comfrey

extract and a pharmaceutical grade tannic acid, 3.5 g/day), or placebo on osteoarthritic knee pain, muscle strength, and markers of inflammation and cartilage breakdown over twelve weeks in participants aged >50 with clinically diagnosed OA and a pain intensity score >40mm on a visual analogue scale (VAS).

A3.2 Methods

A3.2.1 Trial design

This study was a two centre double blind parallel-group placebo controlled randomised trial of topical treatment 4Jointz vs placebo with a 1:1 allocation ratio.

A3.2.2 Settings and locations

Participants were recruited from September 2010 to May 2011 through advertising in local print media in Hobart, Tasmania and Sydney, New South Wales in Australia. Participants attended clinics at either the Menzies Research Institute Tasmania in Hobart, or the Royal North Shore Hospital in Sydney.

A3.2.1.1 Inclusion and exclusion criteria

Participants were aged >50 years, with clinically diagnosed knee OA using ACR criteria (Altman, 1995), and had knee pain on most days of >40mm on a 100mm visual analog scale (VAS) in their worst knee. Participants were excluded if they had knee X-rays with joint space narrowing (JSN) of Grade 3 using the Osteoarthritis Research Society International (OARSI) atlas (Altman, 1986), read by chief investigators (GJ and LM) on diagnostic radiographs; had other forms of arthritis (including hip osteoarthritis); had significant knee injury in the last six months; or were unable to provide informed consent. Participants who were otherwise eligible and those who had Grade 3 JSN in their worst knee were able to enter the study if JSN was <3 in the other knee.

A3.2.3 Participants

Participants were screened over the telephone. If they met the inclusion criteria and did not meet the exclusion criteria, they were invited to attend a

study centre for screening. Screening and examination was undertaken by a rheumatologist (GJ, LM) and a nurse (MC, MG, TF). Participants supplied a blood specimen for serum chemistry, renal function and inflammatory markers; a urine sample for cartilage metabolites; and had a semi-flexed knee X-ray. Use of other medication (including pain medicines) was allowed but kept constant through the trial period where possible. All participants provided written consent. The study was approved by the Human Research Ethics Committee (Tasmania) Network and the Northern Sydney Local Health District Human Research Ethics Committee.

A3.2.4 Interventions

Participants received either 4Jointz cream (active) or identical inert placebo cream. The active treatment was a combination of a standardized comfrey extract (200 mg/g) and pharmaceutical grade tannic acid (100 mg/g) plus other ingredients including aloe vera (300 mg/g), eucalyptus oil (40 mg/g), and frankincense oil (1.0 mg/g).

Participants were instructed to apply enough cream to coat the knee with a thin coating which was then massaged in using gentle circular motions for 3–5 minutes, three times daily. Therefore the daily dose was approximately 3.5 g/day. Participants were supplied with one 100g tube of cream at each visit. Study medication was stored in a locked cupboard prior to dispensing, and dispensed when patients successfully completed the screening visit(s). Treatment continued for twelve weeks, where medication use was discontinued while maintaining the blind. Participants were re-assessed at 16 weeks.

A3.2.5 Outcomes

Primary hypotheses were that 4Jointz was superior to placebo at twelve weeks for change in: knee pain (using the pain intensity VAS and the pain scale from the Knee Injury and Osteoarthritis Outcome Score Questionnaire (KOOS)); markers of inflammation (IL-6), and cartilage breakdown (CTX-2).

Secondary hypotheses were that 4Jointz was superior to placebo for change in: pain between baseline and four and eight weeks of treatment; response using the OARSI response criteria (Pham, 2004), lower limb muscle strength and use of paracetamol between baseline and four, eight and twelve weeks.

A3.2.6 Outcome measures

A3.2.6.1 Pain and function

Knee pain intensity was measured using a 100mm visual analogue scale on four occasions (baseline, four, eight, twelve and sixteen weeks). Participants were asked “on this line, where would you rate your pain today?”.

Knee pain and symptoms were also assessed using the KOOS questionnaire on all five occasions (Roos, 1998). These two subscales have nine (pain) and seven (symptoms) questions, each with five response levels scored from 0–4. Subscales were transformed according to instructions in the original manuscript (Roos, 1998). The transformed scale had possible values from 0–100 with zero representing extreme knee pain or symptoms and 100 representing no knee pain or symptoms. Baseline questionnaires were completed in the clinic. Subsequent questionnaires were completed by mail.

A3.2.6.2 Inflammation and cartilage breakdown

Urine and blood samples were stored at -80°C. Baseline and twelve week urine samples were assayed for the cartilage breakdown marker CTX-II in one batch in duplicate using a Human CTX-2 ELISA kit (Cusabio Biotech Co, Hubei Province, China), and following the manufacturers’ instructions. Urine

was diluted by half, and absorbance was read at 450nm with reference wavelength at 570nm. Samples with <1 ng/mL were deemed out of range and analysed with a value of zero.

Baseline and twelve week blood samples were assayed for the inflammatory marker IL-6 in one batch in duplicate using a Human IL-6 ELISA MAX Deluxe SET kit (Biolegend, California, USA), and following the manufacturers' instructions. Sera was used neat, and absorbance was read at 450nm with reference wavelength at 570nm. Samples with <1 pg/mL were deemed out of range and analysed with a value of zero.

A standard curve was run on each plate, in duplicate ($R^2 > 0.997$).

Absorbance was read using SoftMax Pro software, which calculated the standard curves and concentrations for each unknown on a plate by plate basis.

A3.2.6.3 OMERACT-OARSI response criteria

Response to 4Jointz was assessed using a modified version of the OMERACT-OARSI set of response criteria (Pham, 2004). Participants were classed as responding if they had high improvement in pain (using the VAS) or function (using KOOS function scale) of $\geq 50\%$ and absolute change ≥ 20 ; or if they had improvement in both pain and function of $\geq 20\%$ or ≥ 10 . Criteria for change in participants' global assessment were not included.

A3.2.6.4 Paracetamol usage

Paracetamol usage was recorded at baseline (along with other medication) and at each subsequent visit. For participants who did not use paracetamol daily, the dose taken was averaged to a daily dose over a 28 day month.

A3.2.6.5 Muscle strength

Leg strength was measured to the nearest kilogram in both legs simultaneously, using a dynamometer (TTM Muscular Meter, Tokyo, Japan) as previously described (Scott, 2009). This tests isometric strength, predominantly of the quadriceps and hip extensors.

A3.2.6.6 Safety

Adverse events were defined as any untoward event occurring during the trial regardless of whether it was considered medication-related. Serious adverse events were defined as unplanned hospital admissions, new cancer diagnoses or death during the 16 weeks of the study. Blood tests were performed at baseline and 12 weeks to assess safety, and included general biochemistry, red and white cell parameters and platelet counts.

A3.2.7 Sample size

Sample size for pain intensity using VAS was based on demonstrating a 10mm greater reduction compared to placebo with a SD of 20mm (Langford, 2006; Raynauld, 2004). A change of 10mm reduction on the VAS (compared to placebo) required 62 participants per group with $\alpha=0.05$ and $\beta=0.20$. Therefore, we aimed to enrol 70 participants in each group to allow for dropouts.

A3.2.8 Randomisation and sequence generation

Participants were randomly allocated to one of two treatment arms (4Jointz or placebo) using computer generated block randomisation in blocks of four. The random allocation sequence was automatically generated, and a security protected central automated allocation procedure was used to allocate participants to treatment arm 1 or 2. This was then used by one author (LL, who had no contact with participants) to dispense the allocated medication for the Hobart participants. Research nurses enrolled participants in the trial,

and then gave tubes of cream to each individual patient. The procedure for Sydney patients was the same except that the pharmacy at the Royal North Shore Hospital dispensed allocated medication to Sydney participants. The active treatment and placebo product were visually and aromatically identical. Participants and staff involved in patient care remained blinded to treatment allocation throughout the trial.

A3.2.9 Statistical methods

We used Stata 12.0 (StataCorp LP) for statistical analyses. Statistical significance was set as a p value ≤ 0.05 (two-tailed). We used a modified intent to treat (ITT) approach for data analysis, where all patients who were randomised to receive treatment were included in the analysis. Change in outcomes were assessed using the difference between the factor at baseline and follow up and assessed using linear regression. Normality checks were done using Stata's `pnorm` and `qnorm` functions. Change in CTX-2 and change in IL-6 both had one highly influential outlier ($>99^{\text{th}}$ percentile) which was omitted from analysis in order to satisfy requirements of normality for linear regression. Poisson regression was used to compare numbers of adverse events, with data checked for overdispersion. Change in binary outcomes were assessed using logistic regression for panel data (`xmlogit`) and clustering on ID to account for correlated outcomes within an individual. Post-hoc analyses on the change in outcomes by sex, OARSI grade and BMI were also performed, using linear regression. Sensitivity analyses were performed on estimates of the effect of treatment between baseline and twelve week, adjusting for covariates where there was a statistically or clinically significant difference at baseline (OARSI grade, use of paracetamol, use of glucosamine).

Results

A3.3.1 Study participants

Figure A3. shows that a total of 167 participants attended screening for the study. 34 participants were excluded after initial screening. Most of these (n=30) had knee OA which was too severe (Grade 3 JSN). The remaining 133 participants were randomised to receive either 4Jointz or placebo. After twelve weeks of follow-up (the time at which the main outcomes were assessed), 81% of the cohort had been retained, 88% in the placebo group and fewer patients (75%) in the intervention group (p=0.03).

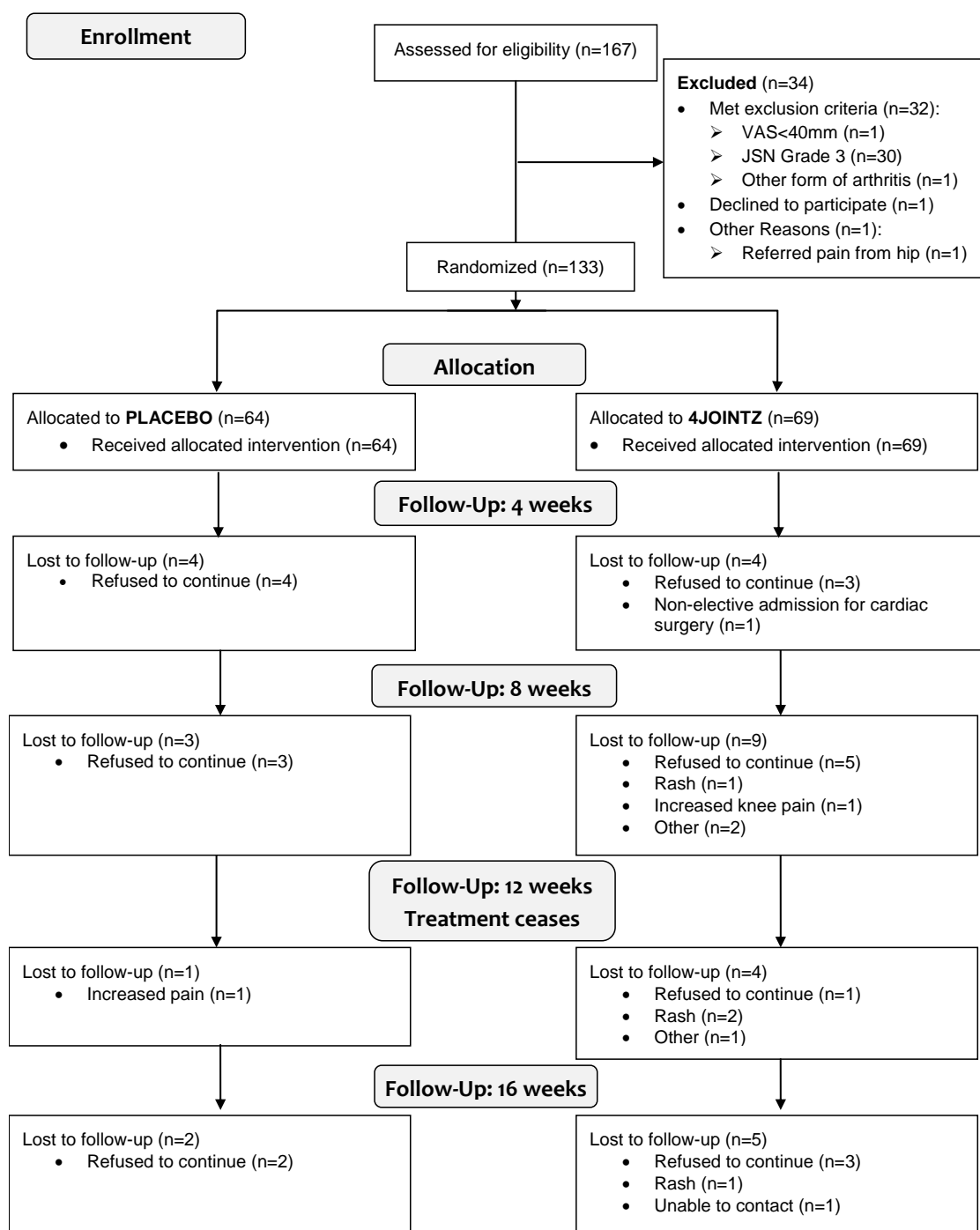


Figure A3.1: Study flow chart

Table A3.1 shows that participants were predominantly middle aged, overweight women. One in eight had experienced previous surgery, and the average pain intensity indicated that these participants were in moderate to

severe pain on most days despite being on up to three different pain medications.

The participants receiving 4Jointz and placebo were well matched. The groups were different in their use of glucosamine ($p=0.04$) and number of pain medicines used ($p=0.049$), which was predominantly differences in use of paracetamol and glucosamine.

Table A3.1: Baseline characteristics of study patients

	4Jointz n=64 mean (sd)	Placebo n=69 mean (sd)
Age	64.3 (9.8)	65.5 (8.3)
Sex (% male)	45	36
Weight	83.3 (15.9)	81.6 (16.6)
BMI	29.7 (4.9)	29.9 (5.1)
Medication use		
Paracetamol (%)	30	41
Average paracetamol dose (mg)	1710 (1374.9)	1475 (1165.7)
Fish oil (%)	30	34
Glucosamine (%)	22	38
COX-2 inhibitors (%)	14	16
Radiographic OA (n, %)*		
Grade 0	12 (17)	18 (28)
Grade 1	24 (35)	13 (20)
Grade 2	22 (32)	21 (33)
Grade 3	0	0
Number of pain medicines (n, %)		
0	31 (45)	16 (25)
1	18 (26)	17 (27)
2	7 (10)	16 (25)
3	13 (19)	15 (23)
Previous knee surgery, self-reported (%)	10	14
Pain intensity (VAS score)	52.7 (15.7)	53.8 (14.5)
Pain intensity (KOOS)	57.0 (12.7)	56.2 (15.5)
Symptoms score (KOOS)	59.6 (14.9)	58.6 (16)
IL-6 (pg/mL)	5.7 (7.2)	6.4 (13.9)
CTX-2 (ng/mL)	20.8 (48.4)	21.5 (38.5)

*Radiographic OA assessed using OARSI criteria

A3.3.2 Outcomes

Data on the main outcomes are shown in Table A3.2. Data was analysed using all available data points.

Primary hypotheses

For the primary hypotheses of changes between baseline and twelve weeks, the data shows that the treated group had an significantly greater reduction in knee pain on the VAS scale averaging 9.9mm ($p=0.034$) compared to placebo. It also showed a significant improvement, 5.7 points on the KOOS pain scale ($p=0.047$). Neither change in IL-6 (-1.6, 95% CI -4.0 to 0.8; $p=0.2$) nor change in cartilage breakdown (2.8, 95% CI -10.6 to 16.1; $p=0.68$) were significantly different between baseline and twelve weeks.

Secondary outcomes

The change in pain recorded using the KOOS pain scale was significantly different by eight weeks, with patients receiving 4Jointz experiencing less pain (6.1, $p=0.025$).

Participants receiving 4Jointz also had greater leg strength (2.9 kg, $p=0.02$) after twelve weeks of treatment, this result remained statistically significant after adjustment for baseline differences.

Table A3.2: Effect of treatment with 4Jointz: study outcomes after four, eight and twelve weeks of treatment, using change models

	4 weeks Beta (95% CI)	p	8 weeks Beta (95% CI)	p	12 weeks Beta (95% CI)	p	16 weeks Beta (95% CI)	p
	n=124		n=112		n=106		n=101	
Pain (VAS)	-3.0 (-10.4 to 4.4)	0.42	-5.7 (-13.8 to 2.3)	0.16	-9.9 (-19.1 to -0.8)	0.034	-2.4 (-11.6 to 6.7)	0.60
Pain (KOOS)	1.3 (-3.3 to 5.9)	0.58	6.1 (0.8 to 11.4)	0.025	5.7 (0.1 to 11.3)	0.047	0.03 (-7 to 7.1)	0.99
Symptoms	1.7 (-2.6 to 6.0)	0.45	-0.2 (-5.3 to 4.9)	0.94	4.7 (-1.3 to 10.7)	0.12	-2.5 (-8.6 to 3.6)	0.43
Leg strength (kg)	-0.02 (-2.4 to 2.4)	0.99	1.9 (-0.6 to 4.5)	0.13	2.9 (0.5 to 5.3)	0.02	1.5 (-1.3 to 4.3)	0.30
IL6	-		-		-1.6 (-4.0 to 0.8)	0.20	-	
CTX-2	-		-		2.8 (-10.6 to 16.1)	0.68	-	
OMERACT-OARSI response criteria*	1.2 (0.7 to 2.1)	0.56	1.4 (0.82 to 2.4)	0.22	1.3 (0.8 to 2.2)	0.34	1.1 (0.7 to 2)	0.63
Paracetamol use (yes / no) ‡	1.0 (0.6 to 1.7)	0.85	1.0 (0.8 to 1.4)	0.82	1.0 (0.8 to 1.2)	0.8	1.0 (0.8 to 1.1)	0.67
Paracetamol dose (in those using at baseline)	-70.7 (-759.9 to 618.6)	0.84	-247.6 (-925.6 to 430.5)	0.46	-404.2 (-1268.8 to 460.4)	0.35	-734.9 (-1615.7 to 145.8)	0.098

The statistics presented are the change in the outcome between baseline and the time point of interest except the response criteria.

The number presented is the beta coefficient (and 95% CI) for the additional effect of treatment over that of placebo except where ‡odds ratios or

*Poisson regression is used, where indicated.

Treatment ceased after twelve weeks.

Table A3.3: Offset effect- change in study outcomes when treatment ceases (between 12 and 16 weeks of observation)

	Beta (95% CI) n=99	p
Pain (VAS)	9.2 (0.4 to 17.9)	0.04
Pain (KOOS)	-6.8 (-13 to -0.5)	0.034
Symptoms	-8.5 (-14.1 to -2.8)	0.004
Leg strength (kg)	-2.5 (-4.9 to -0.1)	0.04
OMERACT-OARSI response criteria [‡]	1.1 (0.7 to 2.0)	0.63
Paracetamol use (yes / no) [‡]	0.2 (0.02 to 1.5)	0.11
Paracetamol dose (in those using at baseline)	-308.9 (-802.8 to 185)	0.21

Statistics presented are the change in the outcome between baseline and the time point of interest except the response criteria. The number presented is the beta coefficient (and 95% CI) for the additional effect of treatment over that of placebo except where [‡]odds ratios or [‡] Poisson regression is used, where indicated.

Paracetamol offset effect (change between 12-16 weeks) is adjusted for baseline paracetamol use

A3.3.3 Individual outcomes

A3.3.3.1 Pain intensity (using visual analog scores)

Figure A3.2 shows that pain intensity decreased in both groups at the beginning of the trial period and plateaus in the placebo group after eight weeks of treatment. By twelve weeks of treatment, difference in the change scores between groups were statistically significant (-9.9 mm, 95% CI -19.1 to -0.8; $p=0.034$), see Table A3.. This remained significant after adjustment for differences in the group at baseline (baseline paracetamol and glucosamine use, and OARSI grade). After the treatment was discontinued, the differences between the groups rapidly reduced (9.2mm (95% CI 0.4 to 17.9); $p=0.04$ (Table A3.3).

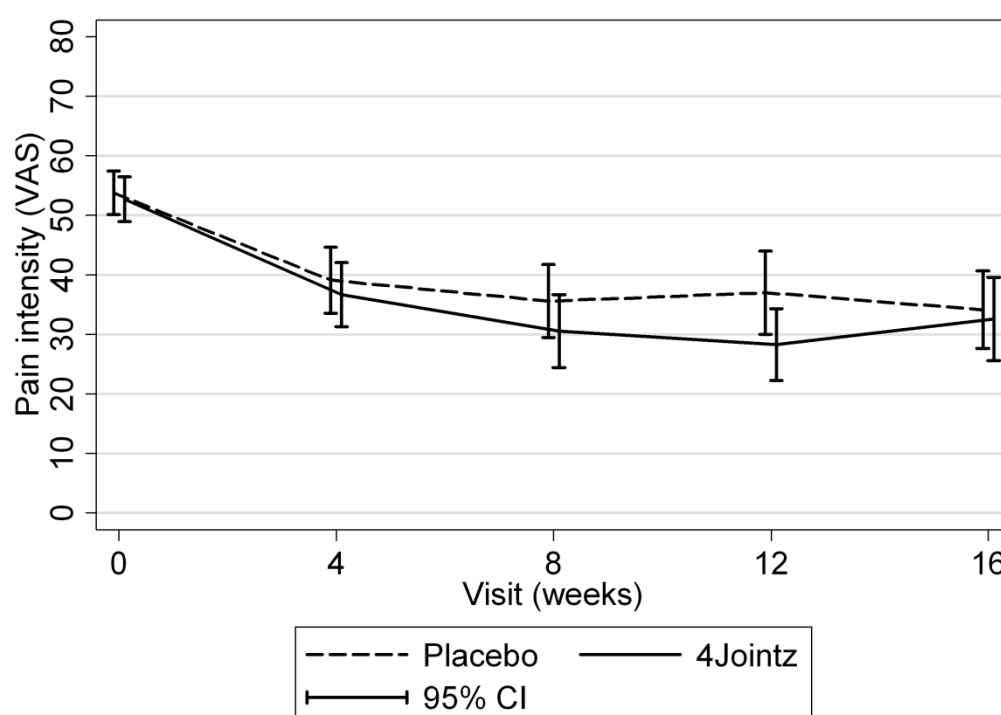


Figure A3.2: Pain intensity (using the visual analog scores) over sixteen weeks of treatment, by treatment received

A3.3.3.2 KOOS results

Figure A3.3 shows that pain intensity (as measured using the KOOS questionnaire) reduced in both groups at the beginning of the trial period (note: “no pain” is zero on the KOOS scale, not 100) and plateaus in the placebo group after four weeks of treatment. By eight weeks of treatment, the difference in the change scores between groups were statistically significant (6.1, 95% CI 0.8 to 11.4; $p=0.025$), this difference remained significant at twelve weeks (5.7, 95% CI 0.1 to 11.3; $p=0.047$), see Table A3.. After adjustment for baseline paracetamol and glucosamine use, and OARSI grade, the effect of treatment was no longer significant, but the magnitude of the effect was similar (5.2, $p=0.12$) and none of the covariates were statistically significant. After the treatment was discontinued, the differences between the groups rapidly decreased (-6.8, 95% CI -13 to -0.5; $p=0.034$, Table A3.3).

For symptoms, differences in change scores between the group receiving placebo and 4Jointz were not statistically significant at any time point, except between twelve and sixteen weeks when the treatment was discontinued (-8.5, -14.1 to -2.8; 0.004).

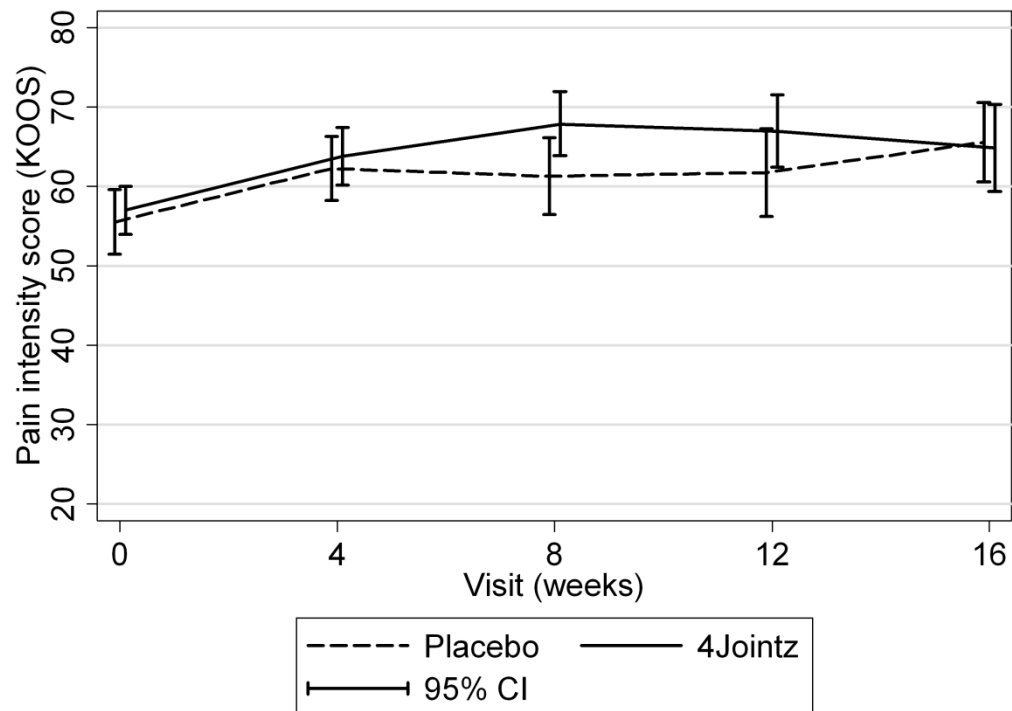


Figure A3.3: Pain intensity (as measured using the KOOS questionnaire) over sixteen weeks of treatment, by treatment received

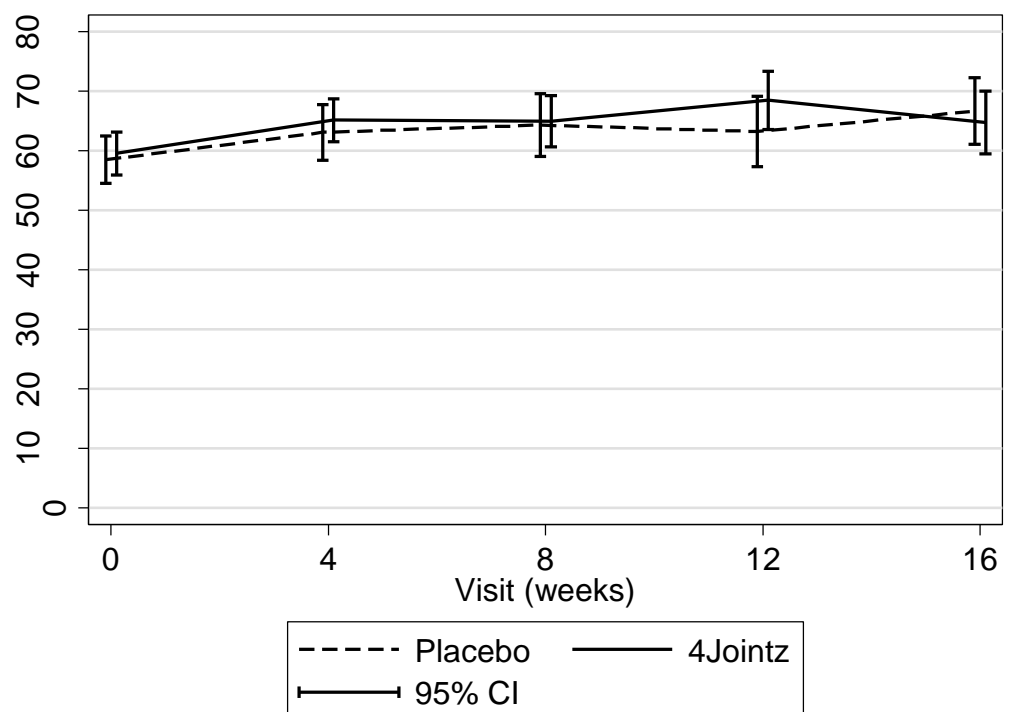


Figure A3.4: Symptom scale, as measured using the KOOS questionnaire, over sixteen weeks of treatment, by treatment received

A3.3.3.3 Cartilage breakdown

Changes in the cartilage breakdown marker CTX-2 were not significant between baseline and twelve weeks (See Table A3.2, Figure A3.5), and remained non-significant after adjusting for baseline differences.

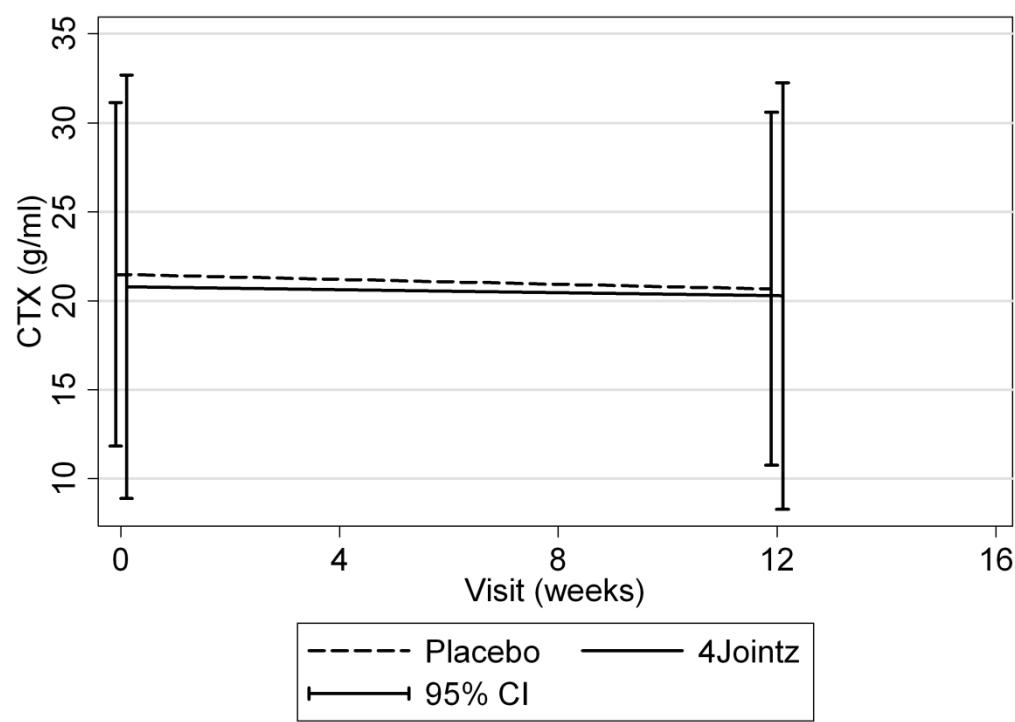


Figure A3.5: CTX-2, by treatment received

A3.3.3.4 Systemic inflammation

Changes in the measure of systemic inflammation (IL-6) were not significant between baseline and twelve weeks (See Table A3.2, Figure A3.6), and remained non-significant after adjusting for baseline differences.

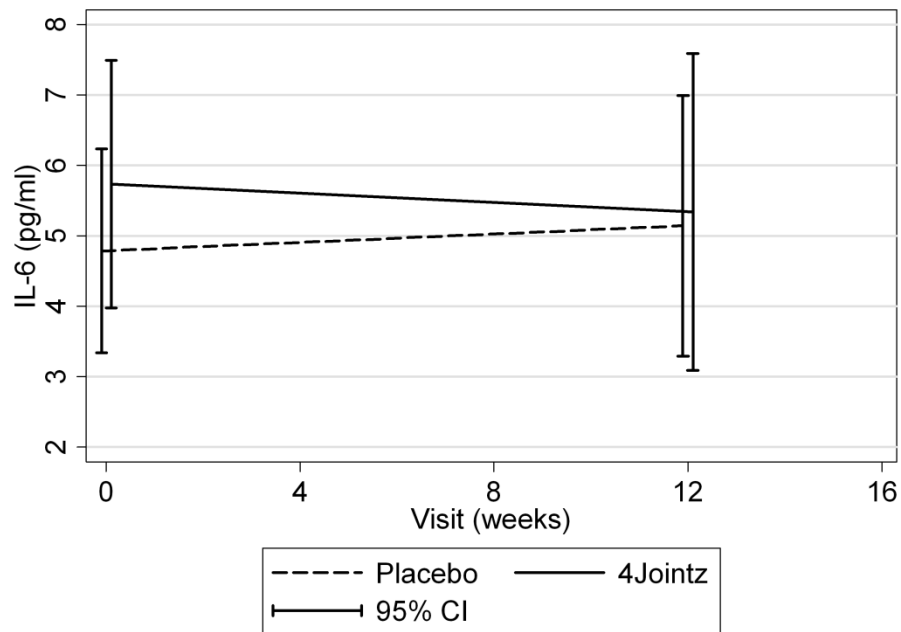


Figure A3.6: IL6, by treatment received

A3.3.3.5 Paracetamol use

Usage of paracetamol was assessed in two ways, firstly whether participants were using paracetamol or not (prevalence of paracetamol use), and daily dose of paracetamol used amongst persons reporting paracetamol use at baseline.

Treatment with 4Jointz did not change prevalence of paracetamol use (using compared to not using) over the duration of the trial, nor did it change when treatment ceased after week 12, after adjustment for baseline paracetamol use ($p=0.11$, Table A3.3). More participants in the placebo group used paracetamol at baseline than persons receiving 4Jointz (see Table A3.2, Figure A3.7), but this difference also did not reach statistical significance ($p=0.09$).

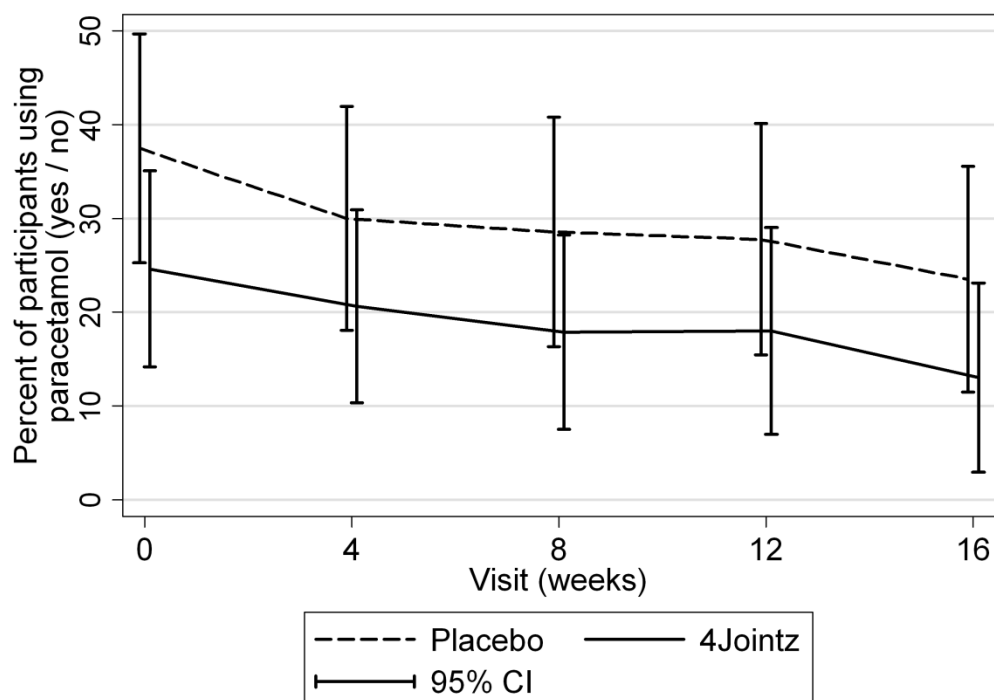


Figure A3.7: Proportion of participants using paracetamol over sixteen weeks of treatment, by treatment received

Figure A3.8 shows that among persons using paracetamol at baseline (n=47) treatment with 4Jointz decreased the daily dose of paracetamol taken over the duration of the trial (weeks 1-12) by 404mg but this did not reach statistical significance (p=0.35). Similarly, daily dose of paracetamol was not different between groups when treatment ceased (week 12-16, see Table A3.3). Variation within the groups (as seen with the 95% confidence intervals of the estimates) was large compared to the observed effect sizes.

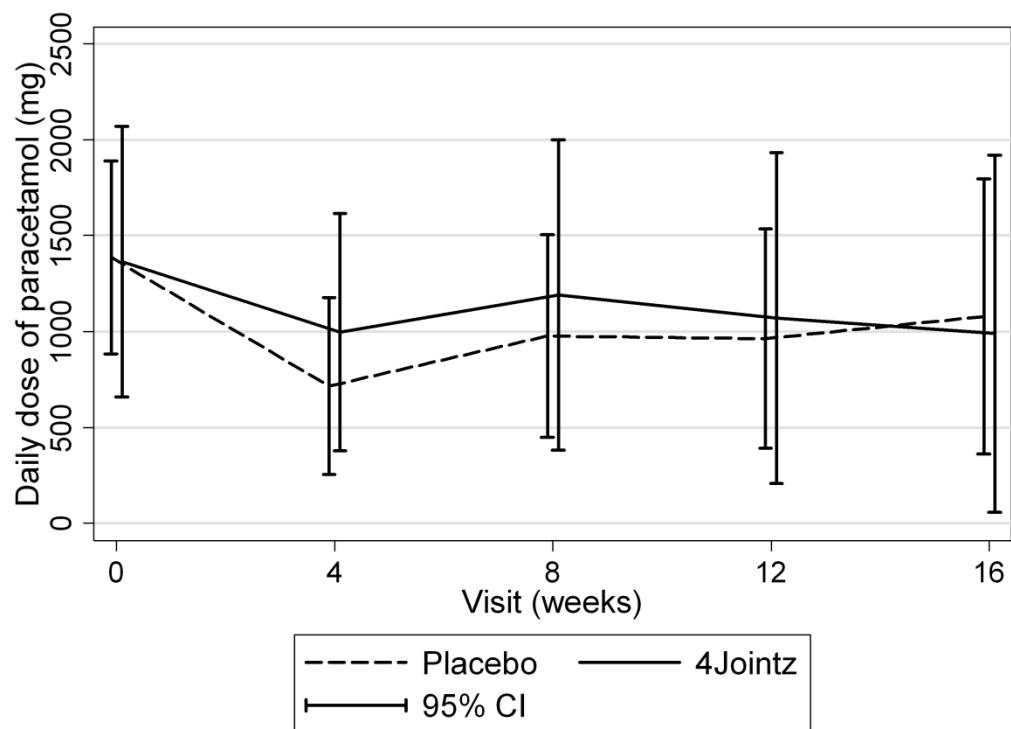


Figure A3.8: Daily dose of paracetamol (mg) over sixteen weeks, in participants using paracetamol at baseline, by treatment received

A3.3.3.6 Leg strength

Figure A3.9 shows that the groups receiving placebo and 4Jointz began to diverge in their leg strength measures by eight weeks, and by twelve weeks the differences in change scores between the two groups had reached statistical significance (2.9, 95% CI 0.5 to 5.3; $p=0.02$), see Table A3.2. Leg strength remained significant after adjustment for baseline differences and reduced when treatment ceased (-2.5kg, $p=0.04$).

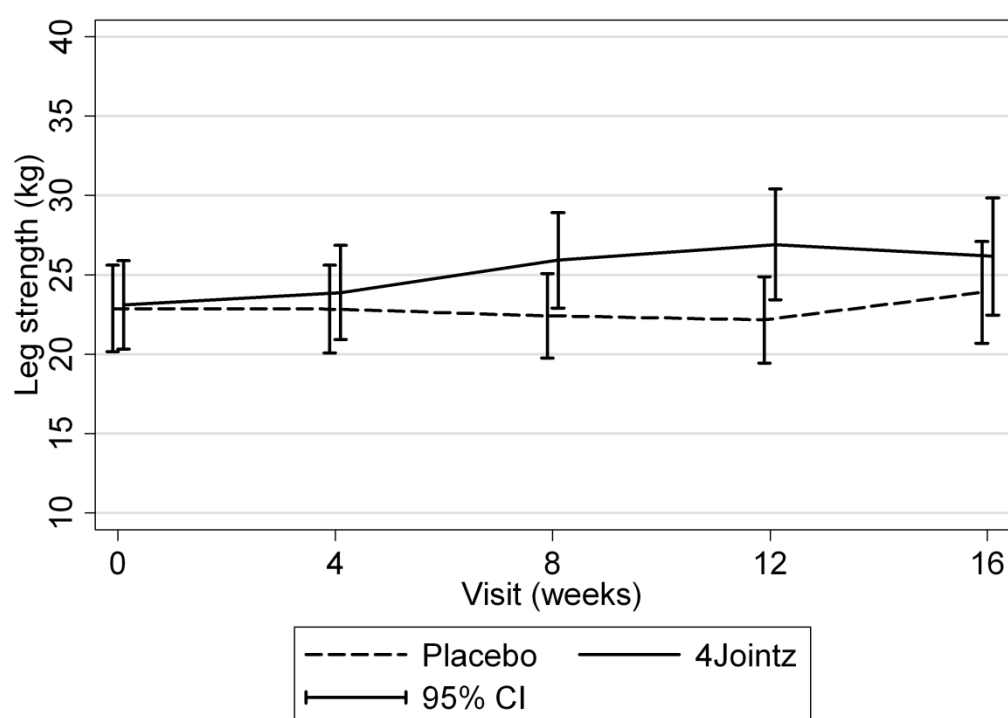


Figure A3.9: Leg strength over sixteen weeks of treatment, by treatment received

A3.3.3.7 OMERACT – OARSI response criteria

Figure A3.10 shows the response to treatment using a modified form of the OMERACT-OARSI response criteria. Response to treatment was not different between participants receiving 4Jointz and placebo, at any time point.

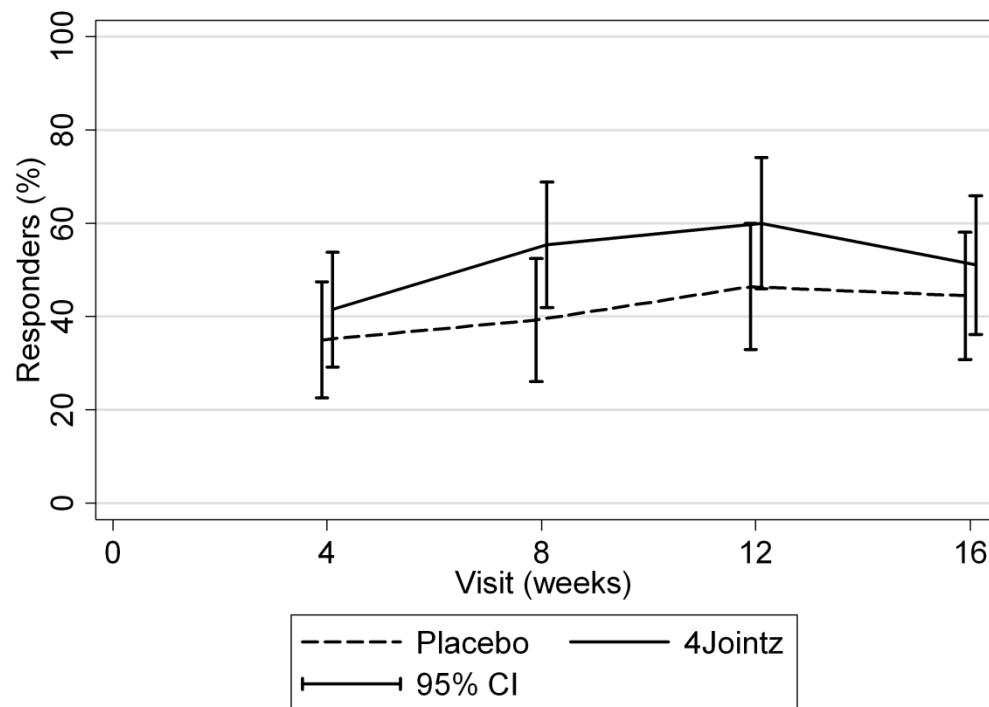


Figure A3.10: Response to treatment using a modified version of the OMERACT – OARSI response criteria, by treatment received

A3.3.4 Post-hoc analyses

Additional analyses were conducted on the pain measures. These were analyses decided after the trial concluded, and are therefore of a hypothesis-generating rather than a hypothesis-answering nature.

A3.3.4.1 Gender

We investigated the effect of treatment with 4Jointz (vs placebo) on pain intensity on men compared to women; persons with different grades of radiographic knee OA, initial pain score (above / below a VAS of 50), and BMI (above / below a BMI of 25).

Women responded better to treatment than men, using both the VAS pain intensity score and the KOOS pain scale (see Table A3.4, Figure A3.11 and Figure A3.12).

Table A3.4: Change in pain scores between baseline and twelve weeks, by gender and treatment group

Change in		n	Placebo	n	4Jointz	Diff	p
VAS score	Females	36	-12.9 (-21.7 to -4.1)	24	-29.7 (-37.1 to -22.2)	-16.8	0.008
	Males	20	-20.4 (-31.8 to -8.9)	26	-21.6 (-31.4 to -11.7)	-1.2	0.87
KOOS pain score	Females	35	1.9 (-2.8 to 6.6)	23	10.6 (5.2 to 16.0)	8.7	0.018
	Males	19	11.0 (6 to 16)	26	10.9 (3.8 to 18.1)	-0.1	0.99

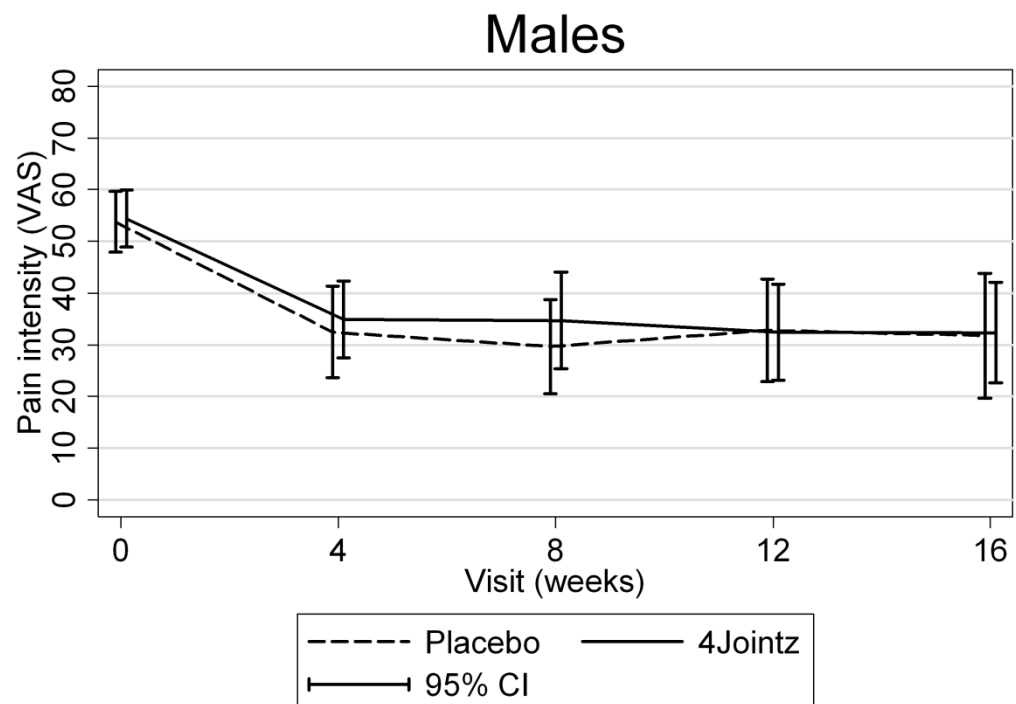
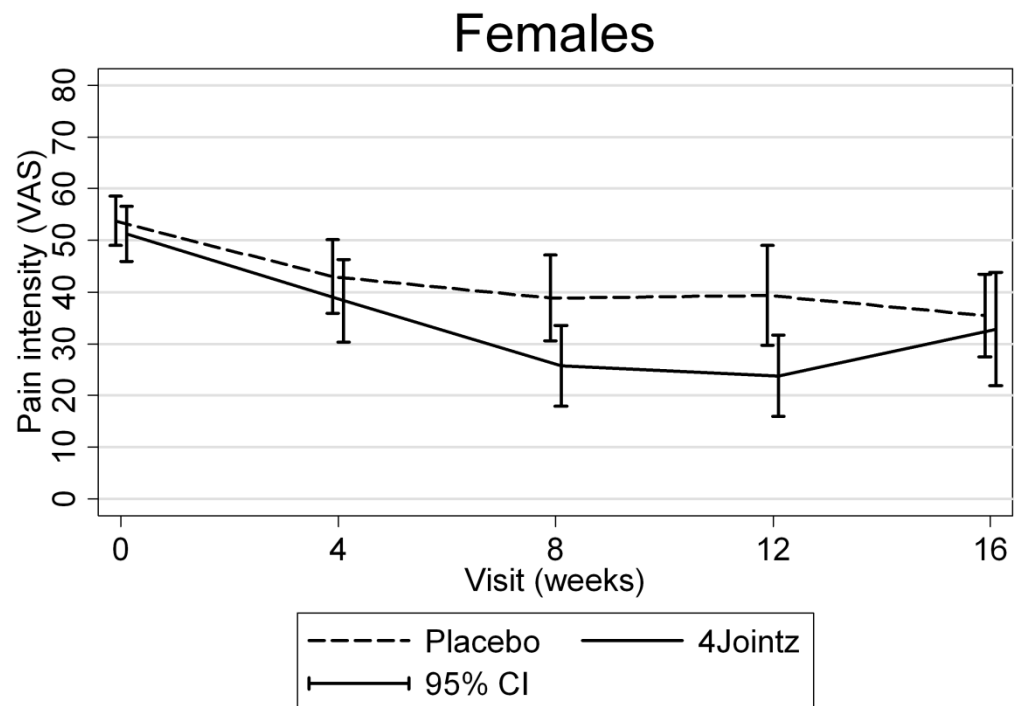


Figure A3.11a and b: Effect of treatment on pain intensity in women and men, by treatment received

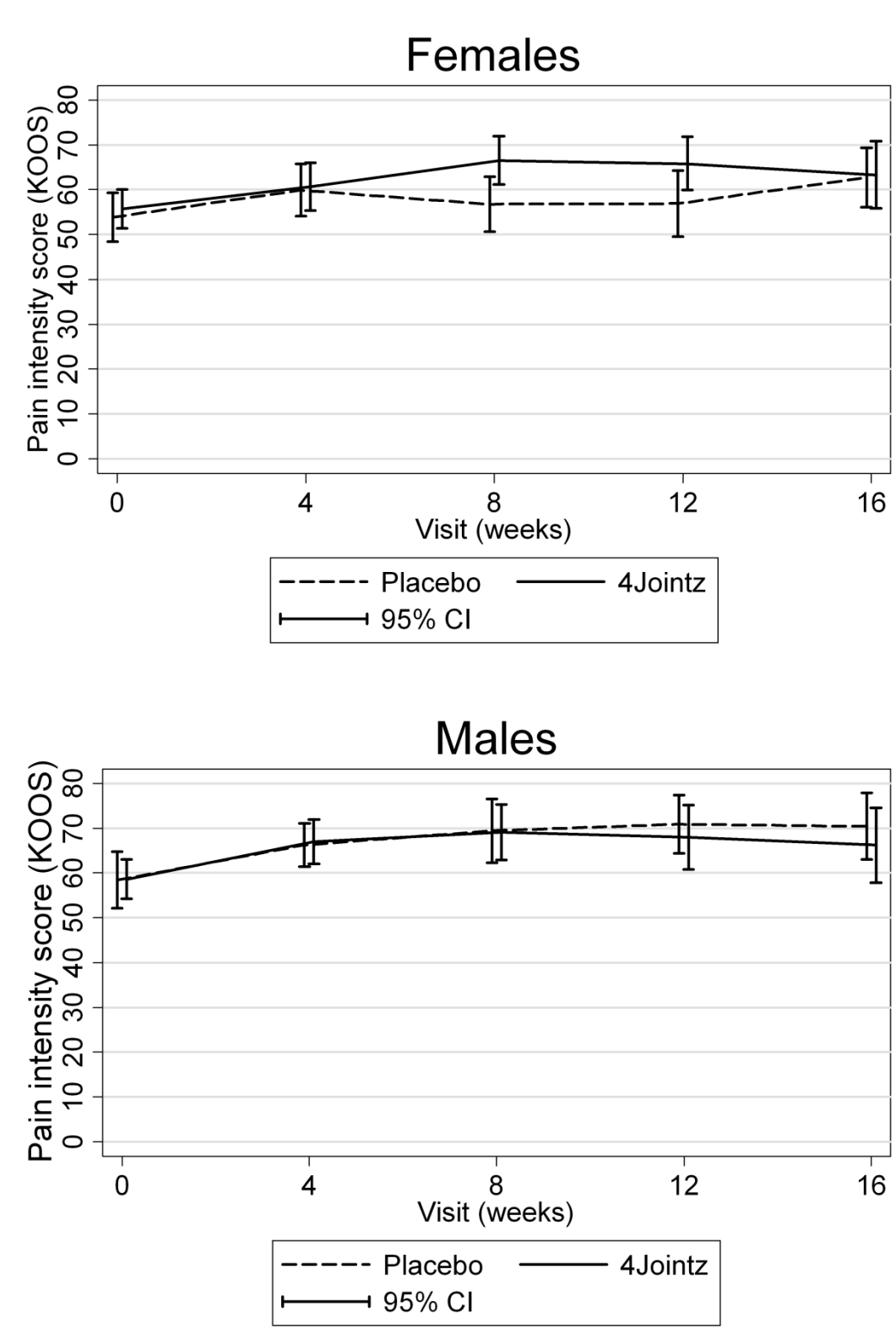


Figure A3.12 a and b: Effect of treatment on KOOS pain score in women and men, by treatment received

A3.3.4.2 OARSI grade and BMI

The effect of treatment by radiographic staging of OA was also investigated, using OARSI grade, and by body mass index (below / above a BMI of 25).

After twelve weeks of treatment, 4Jointz was effective in treating persons with OARSI grades of 0 and 1 but not those with OARSI grade 2 (see Figure A3.13).

Treatment appeared more effective in participants who were overweight or obese, but this did not reach statistical significance. The effect size was similar in participants with BMI below 25 as above 25 so this may merely reflect the smaller number of persons in the healthy weight range in the sample.

Table A3.5: Change in VAS score between baseline and twelve weeks, by OARSI grade and body mass index.

	n	PLACEBO	n	4Jointz	Diff	p
OARSI grade						
0 or 1	29	-9.9 (-20.3 to 0.5)	26	-26.0 (-31.6 to -20.4)	-16.1	0.009
2	17	-22.3 (-33.7 to -10.9)	16	-29.6 (-42 to -17.3)	-7.3	0.36
BMI<25	9	-20.6 (-39.2 to -1.9)	7	-31.1 (-58.6 to -3.7)	-10.6	0.45
BMI 25+	47	-14.6 (-22.2 to -7.0)	41	-24.4 (-30.9 to -17.9)	-9.8	0.06

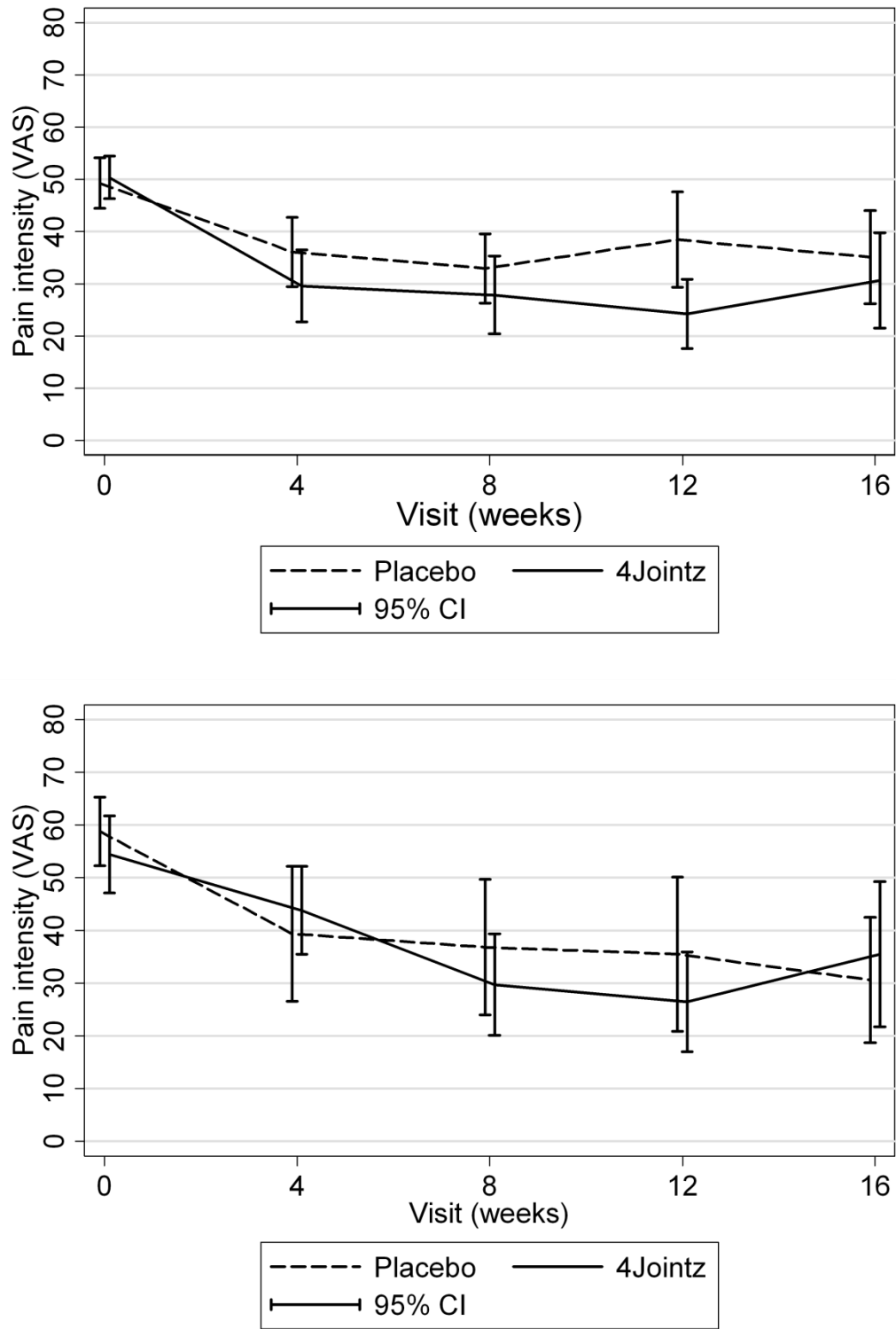


Figure A3.13a and b: Effect of treatment on pain intensity in persons by OARSI grade (0 and 1 vs 2), by treatment received

A3.3.5 Adverse events

Adverse events were common in this cohort, with 61% (n=62) of the placebo group and 72% (n=66) of the 4Jointz group experiencing at least one adverse event. Differences in prevalence and actual number of events were not significant (Table A3.6).

One aspect of the adverse events was significantly different between persons receiving 4Jointz and placebo. Localised skin irritation at the site of application (“rash”) was significantly higher in patients receiving 4Jointz (risk ratio 13.2, p=0.013). Participants experiencing localised irritations were advised to cease using the treatment, then rechallenge with cream after a few weeks. Treatment ceased if the rash recurred. Rashes were severe enough to discontinue the study drug in four participants (26% of those with rash) (Table A3.6). One participant had a serious adverse event, which was a non-elective hospital admission where they received a cardiac stent. We think this is unlikely to be causally related to the use of 4Jointz. Over 40% of participants had at least one change in their blood results between baseline and twelve weeks, but differences between participants receiving 4Jointz and placebo were not significant.

Overall, these results show that 4Jointz is safe and effective amongst 50-80 year old adults with clinical diagnosed knee osteoarthritis. The only adverse event experienced more commonly in persons receiving 4Jointz compared those receiving placebo for knee pain is a localised skin irritation, which recurred in a minority after a break in treatment.

Table A3.6: Prevalence and number of adverse events, by treatment received

	Placebo n=62	4Jointz n=67	p
<u>Adverse events</u>			
Prevalence of at least one adverse event (n, %)	38 (61)	48 (72)	0.47
Number of adverse events	67	78	0.85
Prevalence of (n, %)			
Rash	1 (1.6)	14 (21.2)	0.013
Upper respiratory tract infection	11 (17.7)	10 (15.2)	0.69
GI Upset	4 (6.5)	2 (3)	0.37
Headache	3 (4.8)	6 (9.1)	0.38
Increased knee pain	3 (4.8)	2 (3)	0.60
Knee swelling	1 (1.6)	1 (1.5)	0.96
Abnormal blood results	24 (41)	29 (44)	0.82
Elective hospital admissions	3 (4.8)	1 (1.5)	0.31
<u>Serious adverse events</u>			
Number of non-elective hospital admissions	0	1	
Cancer	0	0	
Death	0	0	

Discussion

This study has demonstrated that 4Jointz is a safe and effective topical treatment for moderate to severe knee OA in participants aged 50-80 years. 4Jointz was effective in reducing pain at twelve weeks using both the VAS and the KOOS scales, and by 8 weeks using the KOOS scale. 4Jointz also increased quadriceps strength by an average of 3 kg after 12 weeks. It had no effect on systemic inflammation or cartilage breakdown over twelve weeks of treatment.

This clinical trial has the longest reported duration of use of comfrey for osteoarthritic knee pain, with previous trials being of three (Grube, 2007) or six weeks duration (Smith and Jacobson, 2011). Patients had the largest responses to treatment at the last occasion during treatment in this study (12 weeks) and therefore if treatment continues past this time, patients may continue to benefit.

Treatment was discontinued after twelve weeks and pain, other symptoms and leg strength significantly worsened. This suggests that there is a rapid offset, and continuing treatment longer than twelve weeks may result in continuing benefit.

The results from this study are consistent with those of two other trials (Grube, 2007; Smith and Jacobson, 2011), in that all support a role for comfrey as a topical treatment for knee pain and OA. However, it is not possible to directly compare results between all studies because the patient populations are different, and the studies use different outcome measures, requiring in-depth analysis of the results to make any reasonable comparisons.

Grube et al (2007) included patients with long term knee pain (not clinically diagnosed OA) and with pain scores (on VAS) as low as 23mm and patients discontinued taking other medications suggesting that participants may not have knee OA, or are earlier in the disease course. The larger effect observed in this study is consistent with our results in early OA. Omitting participants taking analgesics or anti-inflammatory medications would have ruled out nearly 60% participants in the 4Jointz study and thus these results should be seen as an additional benefit of 4Jointz rather than the only benefit. Grube *et al* (2007) also observed a much greater reduction in pain with the use of comfrey than this study at a comparable time point. This may be due to the use of an aggregate of the WOMAC subscales “pain at rest” and “pain on movement”. This is misleading as adding these values is not a representation of either pain scale, does not represent the actual pain levels of the patients and artefactually doubles the apparent magnitude of benefit.

Since post hoc analyses suggested that treatment may be most effective in women and those with milder radiographic osteoarthritis, future research should consider studies specifically in these populations.

We observed clinically important changes in self-rated outcomes in the group receiving placebo as well as those receiving 4Jointz. These were most evident with pain but we also observed them in the KOOS symptom score. This is consistent with a meta-analysis of the placebo effect in clinical trials of treatment for OA (Zhang, 2008), in which effect sizes of 0.26 were reported for placebo in trials of herbal treatments. This highlights the importance of using randomised controlled trials to assess the efficacy of all pharmaceutical treatments.

The side effect profile observed was similar to that reported in a pilot study of 4Jointz (Smith and Jacobson; Grube, 2007). Overall 4Jointz appears safe and well tolerated. Most importantly, the renal toxicity associated with pyrrolizidine-type alkaloids, associated with oral use of comfrey (Stickel and Seitz, 2000) appears absent in topical use, as expected. The skin irritation appears causally related to the use of 4Jointz as it reversed on cessation of treatment, and only reappeared in around one fifth of those with rash.

We supplied participants with one tube of cream per month. We have observed clinically significant changes with one tube of cream per month or about 3.5g/day. Since only one dose of 4Jointz was used in this study we cannot compare with other concentrations. However, Smith et al compared formulations of, 10% and 20% comfrey extract and pseudoplacebo, and whilst both were superior to placebo, the treatment arms were not significantly different from each other (Smith and Jacobson, 2011).

Strengths of this study include the comparatively long duration of treatment, the defined study population and standardised meaningful outcome measures. The major limitation of this study is the difference in dropout rates between the groups receiving placebo and 4Jointz, with more patients ceasing treatment in the 4Jointz group. This included but was not limited to patients who experienced rash and were advised to cease treatment.

Conclusions

Topical treatment using 4Jointz is a safe and effective treatment for the symptoms of OA. In particular, it reduces pain and increases muscle strength, but has no effect on systemic inflammation or cartilage breakdown over twelve weeks of treatment.

Appendix 4: Published manuscripts

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Appendix 4

Contains published article in:

<http://www.biomedcentral.com/1471-2474/13/168>

Laura Laslett, Stephen J Quinn, Tania M Wizenberg, Kristy Sanderson, Flavia Cicuttini, and Graeme Jones. 2012, A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. *BMC Musculoskeletal Disorders*: 13, 168. doi:10.1186/1471-2474-13-168.

Reference List

Reference List

ABS. Disability, Ageing and Carers, Australia. 2003. Canberra: Australian Bureau of Statistics.

ADAMS, J. G., MCALINDON, T., DIMASI, M., CAREY, J. & EUSTACE, S. 1999. Contribution of meniscal extrusion and cartilage loss to joint space narrowing in osteoarthritis. *Clin Radiol*, 54, 502-6.

ADAMSON, J., EBRAHIM, S., DIEPPE, P. & HUNT, K. 2006. Prevalence and risk factors for joint pain among men and women in the West of Scotland Twenty-07 study. *Ann Rheum Dis*, 65, 520-4.

AIGNER, N., PETJE, G., SCHNEIDER, W., MEIZER, R., WLK, M., KOTSARIS, S., KNAHR, K. & LANDSIEDL, F. 2005. Bone marrow edema syndrome of the femoral head: treatment with the prostacyclin analogue iloprost vs. core decompression: an MRI-controlled study. *Wien Klin Wochenschr*, 117, 130-5.

AIHW. Health expenditure for arthritis and musculoskeletal conditions, 2004–05. Arthritis series no. 10. Cat. no. PHE 115. 2009. Canberra: Australian Institute of Health and Welfare. .

AIHW. Australia's health 2010. Australia's health no. 12. Cat. no. AUS 122. Australia's health no. 12, 2010. Canberra: Australian Institute of Health and Welfare.

AL FARAJ, S. & AL MUTAIRI, K. 2003. Vitamin D deficiency and chronic low back pain in Saudi Arabia. *Spine (Phila Pa 1976)*, 28, 177-9.

ALTMAN, R., ASCH, E., BLOCH, D., BOLE, G., BORENSTEIN, D., BRANDT, K., CHRISTY, W., COOKE, T. D., GREENWALD, R., HOCHBERG, M. & ET AL. 1986. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*, 29, 1039-49.

ALTMAN, R. D., HOCHBERG, M., MURPHY, W. A., JR., WOLFE, F. & LEQUESNE, M. 1995. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage*, 3, 3-70.

AMIN, A. R., ATTUR, M., PATEL, R. N., THAKKER, G. D., MARSHALL, P. J., REDISKE, J., STUCHIN, S. A., PATEL, I. R. & ABRAMSON, S. B. 1997. Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. *J Clin Invest*, 99, 1231-7.

ARDEN, N. & NEVITT, M. C. 2006. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol*, 20, 3-25.

BALIKI, M. N., GEHA, P. Y., JABAKHANJI, R., HARDEN, N., SCHNITZER, T. J. & APKARIAN, A. V. 2008. A preliminary fMRI study of analgesic treatment in chronic back pain and knee osteoarthritis. *Mol Pain*, 4, 47.

- BAROJA-MAZO, A. & PELEGRIN, P. 2012. Modulating P2X7 Receptor Signaling during Rheumatoid Arthritis: New Therapeutic Approaches for Bisphosphonates. *Journal of osteoporosis*, 2012, Article ID 408242.
- BECK, T. J., PETIT, M. A., WU, G., LEBOFF, M. S., CAULEY, J. A. & CHEN, Z. 2009. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. *J Bone Miner Res*, 24, 1369-79.
- BEDSON, J. & CROFT, P. R. 2008. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord*, 9, 116.
- BELLAMY, N., BUCHANAN, W. W., GOLDSMITH, C. H., CAMPBELL, J. & STITT, L. W. 1988. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*, 15, 1833-40.
- BENITO, M. J., VEALE, D. J., FITZGERALD, O., VAN DEN BERG, W. B. & BRESNIHAN, B. 2005. Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis*, 64, 1263-7.
- BERRIGAN, F., SIMONEAU, M., TREMBLAY, A., HUE, O. & TEASDALE, N. 2006. Influence of obesity on accurate and rapid arm movement performed from a standing posture. *Int J Obes (Lond)*, 30, 1750-7.
- BERTHIAUME, M. J., RAYNAULD, J. P., MARTEL-PELLETIER, J., LABONTE, F., BEAUDOIN, G., BLOCH, D. A., CHOQUETTE, D., HARAOU, B., ALTMAN, R. D., HOCHBERG, M., MEYER, J. M., CLINE, G. A. & PELLETIER, J. P. 2005. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. *Ann Rheum Dis*, 64, 556-63.
- BIJLSMA, J. W., BERENBAUM, F. & LAFEBER, F. P. 2011. Osteoarthritis: an update with relevance for clinical practice. *Lancet*, 377, 2115-26.
- BINGHAM, C. O., 3RD, BUCKLAND-WRIGHT, J. C., GARNERO, P., COHEN, S. B., DOUGADOS, M., ADAMI, S., CLAUW, D. J., SPECTOR, T. D., PELLETIER, J. P., RAYNAULD, J. P., STRAND, V., SIMON, L. S., MEYER, J. M., CLINE, G. A. & BEARY, J. F. 2006. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum*, 54, 3494-507.
- BIRRELL, F., LUNT, M., MACFARLANE, G. J. & SILMAN, A. J. 2005. Defining hip pain for population studies. *Ann Rheum Dis*, 64, 95-8.
- BLACK, D. M., DELMAS, P. D., EASTELL, R., REID, I. R., BOONEN, S., CAULEY, J. A., COSMAN, F., LAKATOS, P., LEUNG, P. C., MAN, Z., MAUTALEN, C., MESENBRINK, P., HU, H., CAMINIS, J., TONG, K., ROSARIO-JANSEN, T., KRASNOW, J., HUE, T. F., SELLMAYER, D.,

- ERIKSEN, E. F. & CUMMINGS, S. R. 2007. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*, 356, 1809-22.
- BLEAKLEY, C. M., MCDONOUGH, S. M. & MACAULEY, D. C. 2008. Some conservative strategies are effective when added to controlled mobilisation with external support after acute ankle sprain: a systematic review. *Aust J Physiother*, 54, 7-20.
- BLOCK, S. R. 2004. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc*, 79, 1585-6; author reply 1586-7.
- BOLAND, R. 1986. Role of vitamin D in skeletal muscle function. *Endocr Rev*, 7, 434-48.
- BOMBARDIER, C., LAINE, L., REICIN, A., SHAPIRO, D., BURGOS-VARGAS, R., DAVIS, B., DAY, R., FERRAZ, M. B., HAWKEY, C. J., HOCHBERG, M. C., KVIEN, T. K. & SCHNITZER, T. J. 2000. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*, 343, 1520-8.
- BOUTRY, N., PAUL, C., LEROY, X., FREDOUX, D., MIGAUD, H. & COTTEN, A. 2002. Rapidly destructive osteoarthritis of the hip: MR imaging findings. *Am J Roentgenol*, 179, 657-63.
- BRANDT, K. D., DIEPPE, P. & RADIN, E. L. 2008. Etiopathogenesis of osteoarthritis. *Rheum Dis Clin North Am*, 34, 531-59.
- BRANDT, K. D., MAZZUCA, S. A., KATZ, B. P., LANE, K. A., BUCKWALTER, K. A., YOCUM, D. E., WOLFE, F., SCHNITZER, T. J., MORELAND, L. W., MANZI, S., BRADLEY, J. D., SHARMA, L., ODDIS, C. V., HUGENBERG, S. T. & HECK, L. W. 2005. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum*, 52, 2015-25.
- BRESALIER, R. S., SANDLER, R. S., QUAN, H., BOLOGNESE, J. A., OXENIUS, B., HORGAN, K., LINES, C., RIDDELL, R., MORTON, D., LANAS, A., KONSTAM, M. A. & BARON, J. A. 2005. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*, 352, 1092-102.
- BRITT, H., MILLER, G. C., CHARLES, J., HENDERSON, J., BAYRAM, C., PAN, Y., VALENTI, L., HARRISON, C., O'HALLORAN, J. & FAHRIDIN, S. General practice activity in Australia 2009–10. General practice series, no. 27. Cat. no. GEP 27, 2010. Canberra:AIHW.
- BRUYERE, O., DELFERRIERE, D., ROUX, C., WARK, J. D., SPECTOR, T., DEVOGELAER, J. P., BRIXEN, K., ADAMI, S., FECHTENBAUM, J., KOLTA, S. & REGINSTER, J. Y. 2008. Effects of strontium ranelate on spinal osteoarthritis progression. *Ann Rheum Dis*, 67, 335-9.

BRUYERE, O., HONORE, A., ROVATI, L. C., GIACOVELLI, G., HENROTIN, Y. E., SEIDEL, L. & REGINSTER, J. Y. 2002. Radiologic features poorly predict clinical outcomes in knee osteoarthritis. *Scand J Rheumatol*, 31, 13-6.

BRUYNESTEYN, K., VAN DER HEIJDE, D., BOERS, M., SAUDAN, A., PELOSO, P., PAULUS, H., HOUBEN, H., GRIFFITHS, B., EDMONDS, J., BRESNIHAN, B., BOONEN, A. & VAN DER LINDEN, S. 2002. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. *J Rheumatol*, 29, 2306-12.

BUCKLAND-WRIGHT, J. C., MESSENT, E. A., BINGHAM, C. O., 3RD, WARD, R. J. & TONKIN, C. 2007. A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients. *Rheumatology (Oxford)*, 46, 257-64.

CAO, Y., JONES, G., CICUTTINI, F., WINZENBERG, T., WLUKA, A., SHARMAN, J., NGUO, K. & DING, C. 2012. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. *Trials*, 13, 131.

CARBONE, L. D., NEVITT, M. C., WILDY, K., BARROW, K. D., HARRIS, F., FELSON, D., PETERFY, C., VISSER, M., HARRIS, T. B., WANG, B. W. & KRITCHEVSKY, S. B. 2004. The relationship of antiresorptive drug use to structural findings and symptoms of knee osteoarthritis. *Arthritis Rheum*, 50, 3516-25.

CARTER, K. N., IMLACH-GUNASEKARA, F., MCKENZIE, S. K. & BLAKELY, T. 2012. Differential loss of participants does not necessarily cause selection bias. *Aust N Z J Public Health*, 36, 218-22.

CAUGHEY, G. E., ROUGHEAD, E. E., PRATT, N., KILLER, G. & GILBERT, A. L. 2011. Stroke risk and NSAIDs: an Australian population-based study. *Med J Aust*, 195, 525-9.

CHO, M. L., HEO, Y. J., PARK, M. K., OH, H. J., PARK, J. S., WOO, Y. J., JU, J. H., PARK, S. H., KIM, H. Y. & MIN, J. K. 2009. Grape seed proanthocyanidin extract (GSPE) attenuates collagen-induced arthritis. *Immunol Lett*, 124, 102-10.

CIBERE, J. 2006. Do we need radiographs to diagnose osteoarthritis? *Best Pract Res Clin Rheumatol*, 20, 27-38.

CICUTTINI, F., FORBES, A., MORRIS, K., DARLING, S., BAILEY, M. & STUCKEY, S. 1999. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis Cartilage*, 7, 265-71.

CICUTTINI, F. M., JONES, G., FORBES, A. & WLUKA, A. E. 2004. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. *Ann Rheum Dis*, 63, 1124-7.

- CONAGHAN, P. G., D'AGOSTINO, M. A., LE BARS, M., BARON, G., SCHMIDELY, N., WAKEFIELD, R., RAVAUD, P., GRASSI, W., MARTIN-MOLA, E., SO, A., BACKHAUS, M., MALAISE, M., EMERY, P. & DOUGADOS, M. 2010. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. *Ann Rheum Dis*, 69, 644-7.
- CONAGHAN, P. G., HUNTER, D. J., MAILLEFERT, J. F., REICHMANN, W. M. & LOSINA, E. 2011. Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group. *Osteoarthritis Cartilage*, 19, 606-10.
- COOPER, C., O'NEILL, T. & SILMAN, A. 1993. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. *Bone*, 14, S89-97.
- CORBEIL, P., SIMONEAU, M., RANCOURT, D., TREMBLAY, A. & TEASDALE, N. 2001. Increased risk for falling associated with obesity: mathematical modeling of postural control. *IEEE Trans Neural Syst Rehabil Eng*, 9, 126-36.
- CREAMER, P. & HOCHBERG, M. C. 1997. Osteoarthritis. *Lancet*, 350, 503-8.
- CREAMER, P., HUNT, M. & DIEPPE, P. 1996. Pain mechanisms in osteoarthritis of the knee: effect of intraarticular anesthetic. *J Rheumatol*, 23, 1031-6.
- CREAMER, P., LETHBRIDGE-CEJKU, M. & HOCHBERG, M. C. 1999. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. *J Rheumatol*, 26, 1785-92.
- CREAMER, P., LETHBRIDGE-CEJKU, M. & HOCHBERG, M. C. 2000. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology (Oxford)*, 39, 490-6.
- CROFT, P., JORDAN, K. & JINKS, C. 2005. "Pain elsewhere" and the impact of knee pain in older people. *Arthritis Rheum*, 52, 2350-4.
- CROFT, P. R. & RIGBY, A. S. 1994. Socioeconomic influences on back problems in the community in Britain. *J Epidemiol Community Health*, 48, 166-70.
- D'ANCHISE, R., BULITTA, M. & GIANNETTI, B. 2007. Comfrey extract ointment in comparison to diclofenac gel in the treatment of acute unilateral ankle sprains (distortions). *Arzneimittelforschung*, 57, 712-6.
- DAHAGHIN, S., BIERMA-ZEINSTRA, S. M., HAZES, J. M. & KOES, B. W. 2006. Clinical burden of radiographic hand osteoarthritis: a systematic appraisal. *Arthritis Rheum*, 55, 636-47.
- DAHAGHIN, S., BIERMA-ZEINSTRA, S. M., REIJMAN, M., POLS, H. A., HAZES, J. M. & KOES, B. W. 2005. Prevalence and determinants of one

month hand pain and hand related disability in the elderly (Rotterdam study). *Ann Rheum Dis*, 64, 99-104.

DANIELL, H. W. 1976. Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. *Arch Intern Med*, 136, 298-304.

DANIELS, S. R., KHOURY, P. R. & MORRISON, J. A. 2000. Utility of different measures of body fat distribution in children and adolescents. *Am J Epidemiol*, 152, 1179-84.

DAVIES-TUCK, M. L., WLUKA, A. E., FORBES, A., WANG, Y., ENGLISH, D. R., GILES, G. G., O'SULLIVAN, R. & CICUTTINI, F. M. 2010. Development of bone marrow lesions is associated with adverse effects on knee cartilage while resolution is associated with improvement--a potential target for prevention of knee osteoarthritis: a longitudinal study. *Arthritis Res Ther*, 12, R10.

DAVIES-TUCK, M. L., WLUKA, A. E., WANG, Y., ENGLISH, D. R., GILES, G. G. & CICUTTINI, F. 2009. The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. *Ann Rheum Dis*, 68, 904-8.

DAWSON, J., LINSELL, L., ZONDERVAN, K., ROSE, P., RANDALL, T., CARR, A. & FITZPATRICK, R. 2004. Epidemiology of hip and knee pain and its impact on overall health status in older adults. *Rheumatology (Oxford)*, 43, 497-504.

DE LAET, C., KANIS, J. A., ODEN, A., JOHANSON, H., JOHNNELL, O., DELMAS, P., EISMAN, J. A., KROGER, H., FUJIWARA, S., GARNERO, P., MCCLOSKEY, E. V., MELLSTROM, D., MELTON, L. J., 3RD, MEUNIER, P. J., POLS, H. A., REEVE, J., SILMAN, A. & TENENHOUSE, A. 2005. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int*, 16, 1330-8.

DE ROOS, A., KRESSEL, H., SPRITZER, C. & DALINKA, M. 1987. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. *Am J Roentgenol*, 149, 531-4.

DE TORRENTE DE LA JARA, G., PECOUD, A. & FAVRAT, B. 2004. Musculoskeletal pain in female asylum seekers and hypovitaminosis D3. *BMJ*, 329, 156-7.

DIAMOND, T. H., EISMAN, J. A., MASON, R. S., NOWSON, C. A., PASCO, J. A., SAMBROOK, P. N. & WARK, J. D. 2005. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *Med J Aust*, 182, 281-5.

DIEPPE, P. A. & LOHMANDER, L. S. 2005. Pathogenesis and management of pain in osteoarthritis. *Lancet*, 365, 965-73.

- DIEPPE, P. A., SATHAPATAYAVONGS, B., JONES, H. E., BACON, P. A. & RING, E. F. 1980. Intra-articular steroids in osteoarthritis. *Rheumatol Rehabil*, 19, 212-7.
- Dietary reference intakes for calcium and vitamin D. 2010. Washington, DC:Institute of Medicine (US).
- DIMITRI, P., WALES, J. K. & BISHOP, N. 2010. Fat and bone in children: differential effects of obesity on bone size and mass according to fracture history. *J Bone Miner Res*, 25, 527-36.
- DING, C., CICUTTINI, F., PARAMESWARAN, V., BURGESS, J., QUINN, S. & JONES, G. 2009. Serum levels of vitamin D, sunlight exposure, and knee cartilage loss in older adults: the Tasmanian older adult cohort study. *Arthritis Rheum*, 60, 1381-9.
- DING, C., GARNERO, P., CICUTTINI, F., SCOTT, F., COOLEY, H. & JONES, G. 2005. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. *Osteoarthritis Cartilage*, 13, 198-205.
- DING, C., MARTEL-PELLETIER, J., PELLETIER, J. P., ABRAM, F., RAYNAULD, J. P., CICUTTINI, F. & JONES, G. 2008. Two-year prospective longitudinal study exploring the factors associated with change in femoral cartilage volume in a cohort largely without knee radiographic osteoarthritis. *Osteoarthritis Cartilage*, 16, 443-9.
- DIRCKX, J. H. (ed.) 1997. *Stedman's concise medical and allied health dictionary*, Dayton, Ohio: Williams & Wilkins.
- DOMINICK, K. L., AHERN, F. M., GOLD, C. H. & HELLER, D. A. 2004. Health-related quality of life and health service use among older adults with osteoarthritis. *Arthritis Rheum*, 51, 326-31.
- DORE, D., DE HOOG, J., GILES, G., DING, C., CICUTTINI, F. & JONES, G. 2012. A longitudinal study of the association between dietary factors, serum lipids, and bone marrow lesions of the knee. *Arthritis Res Ther*, 14, R13.
- DORE, D., QUINN, S., DING, C., WINZENBERG, T., ZHAI, G., CICUTTINI, F. & JONES, G. 2010. Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. *Arthritis Res Ther*, 12, R223.
- DORR, D. A., JONES, S. S., BURNS, L., DONNELLY, S. M., BRUNKER, C. P., WILCOX, A. & CLAYTON, P. D. 2006. Use of health-related, quality-of-life metrics to predict mortality and hospitalizations in community-dwelling seniors. *J Am Geriatr Soc*, 54, 667-73.
- DUNCAN, R., PEAT, G., THOMAS, E., HAY, E., MCCALL, I. & CROFT, P. 2007. Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be? *Ann Rheum Dis*, 66, 86-91.
- DUNSTAN, D. W., ZIMMET, P. Z., WELBORN, T. A., CAMERON, A. J., SHAW, J., DE COURTEN, M., JOLLEY, D. & MCCARTY, D. J. 2002. The

Australian Diabetes, Obesity and Lifestyle Study (AusDiab)--methods and response rates. *Diabetes Res Clin Pract*, 57, 119-29.

EASTELL, R., CEDEL, S. L., WAHNER, H. W., RIGGS, B. L. & MELTON, L. J., 3RD 1991. Classification of vertebral fractures. *J Bone Miner Res*, 6, 207-15.

EDELSTEIN, S. L. & BARRETT-CONNOR, E. 1993. Relation between body size and bone mineral density in elderly men and women. *Am J Epidemiol*, 138, 160-9.

EDWARDS, R. R., BINGHAM, C. O., 3RD, BATHON, J. & HAYTHORNTHWAITE, J. A. 2006. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Rheum*, 55, 325-32.

ENSRUD, K. E., LIPSCHUTZ, R. C., CAULEY, J. A., SEELEY, D., NEVITT, M. C., SCOTT, J., ORWOLL, E. S., GENANT, H. K. & CUMMINGS, S. R. 1997. Body size and hip fracture risk in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Am J Med*, 103, 274-80.

ESENYEL, M., ICAGASIOGLU, A. & ESENYEL, C. Z. 2012. Effects of calcitonin on knee osteoarthritis and quality of life[epub ahead of print]. *Rheumatol Int*.

FELSON, D. T., CHAISSON, C. E., HILL, C. L., TOTTERMAN, S. M., GALE, M. E., SKINNER, K. M., KAZIS, L. & GALE, D. R. 2001. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med*, 134, 541-9.

FELSON, D. T., LAWRENCE, R. C., DIEPPE, P. A., HIRSCH, R., HELMICK, C. G., JORDAN, J. M., KINGTON, R. S., LANE, N. E., NEVITT, M. C., ZHANG, Y., SOWERS, M., MCALINDON, T., SPECTOR, T. D., POOLE, A. R., YANOVSKI, S. Z., ATESHIAN, G., SHARMA, L., BUCKWALTER, J. A., BRANDT, K. D. & FRIES, J. F. 2000. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med*, 133, 635-46.

FELSON, D. T., MCLAUGHLIN, S., GOGGINS, J., LAVALLEY, M. P., GALE, M. E., TOTTERMAN, S., LI, W., HILL, C. & GALE, D. 2003. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med*, 139, 330-6.

FELSON, D. T., NIU, J., GUERMAZI, A., ROEMER, F., ALIABADI, P., CLANCY, M., TORNER, J., LEWIS, C. E. & NEVITT, M. C. 2007. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum*, 56, 2986-92.

FERRAR, L., JIANG, G., ADAMS, J. & EASTELL, R. 2005. Identification of vertebral fractures: an update. *Osteoporos Int*, 16, 717-28.

FERRAR, L., JIANG, G., ARMBRECHT, G., REID, D. M., ROUX, C., GLUER, C. C., FELSENBURG, D. & EASTELL, R. 2007. Is short vertebral height always an osteoporotic fracture? The Osteoporosis and Ultrasound Study (OPUS). *Bone*, 41, 5-12.

- FERRAR, L., ROUX, C., REID, D. M., FELSENBURG, D., GLUER, C. C. & EASTELL, R. 2011. Prevalence of non-fracture short vertebral height is similar in premenopausal and postmenopausal women: the osteoporosis and ultrasound study. *Osteoporos Int*.
- FLEGAL, K. M., CARROLL, M. D., OGDEN, C. L. & CURTIN, L. R. 2010. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*, 303, 235-41.
- FOLEY, S. J., LORD, S. R., SRIKANTH, V., COOLEY, H. & JONES, G. 2006. Falls risk is associated with pain and dysfunction but not radiographic osteoarthritis in older adults: Tasmanian Older Adult Cohort study. *Osteoarthritis Cartilage*, 14, 533-9.
- FORTIER, L. A. & NIXON, A. J. 1997. Distributional changes in substance P nociceptive fiber patterns in naturally osteoarthritic articulations. *J Rheumatol*, 24, 524-30.
- FOULKES, T. & WOOD, J. N. 2008. Pain genes. *PLoS Genet*, 4, e1000086.
- FUJITA, T., FUJII, Y., OKADA, S. F., MIYAUCHI, A. & TAKAGI, Y. 2001. Analgesic effect of etidronate on degenerative joint disease. *J Bone Miner Metab*, 19, 251-6.
- FUJITA, T., OHUE, M., FUJII, Y., MIYAUCHI, A. & TAKAGI, Y. 2009. Comparison of the analgesic effects of bisphosphonates: etidronate, alendronate and risedronate by electroalgometry utilizing the fall of skin impedance. *J Bone Miner Metab*, 27, 234-9.
- GILL, T. K. & HILL, C. L. 2012. Socioeconomic factors and total joint replacement: comment on the article by Mnatzaganian et al. *Arthritis Rheum*, 64, 1299-300; author reply 1300-1.
- GLOTH, F. M., 3RD, LINDSAY, J. M., ZELESNICK, L. B. & GREENOUGH, W. B., 3RD 1991. Can vitamin D deficiency produce an unusual pain syndrome? *Arch Intern Med*, 151, 1662-4.
- GLOVER, T. L., GOODIN, B. R., HORGAS, A. L., KINDLER, L. L., KING, C. D., SIBILLE, K. T., PELOQUIN, C. A., RILEY, J. L., 3RD, STAUD, R., BRADLEY, L. A. & FILLINGIM, R. B. 2012. Vitamin D, race, and experimental pain sensitivity in older adults with knee osteoarthritis[epub before publication]. *Arthritis Rheum*.
- GNUDI, S., SITTA, E. & LISI, L. 2009. Relationship of body mass index with main limb fragility fractures in postmenopausal women. *J Bone Miner Metab*, 27, 479-84.
- GOSS, J. Projection of Australian health care expenditure by disease, 2003 to 2033. Cat. no. HWE 43. 2008. Canberra:AIHW.
- GOSSEC, L., TUBACH, F., BARON, G., RAVAUD, P., LOGEART, I. & DOUGADOS, M. 2005. Predictive factors of total hip replacement due to primary osteoarthritis: a prospective 2 year study of 505 patients. *Ann Rheum Dis*, 64, 1028-32.

- GOULDING, A., JONES, I. E., TAYLOR, R. W., MANNING, P. J. & WILLIAMS, S. M. 2000. More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res*, 15, 2011-8.
- GRANT, J. F., TAYLOR, A. W., RUFFIN, R. E., WILSON, D. H., PHILLIPS, P. J., ADAMS, R. J. & PRICE, K. 2009. Cohort Profile: The North West Adelaide Health Study (NWAHS). *Int J Epidemiol*, 38, 1479-86.
- GRUBE, B., GRUNWALD, J., KRUG, L. & STAIGER, C. 2007. Efficacy of a comfrey root (*Symphyti offic. radix*) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine*, 14, 2-10.
- GUCCIONE, A. A., FELSON, D. T. & ANDERSON, J. J. 1990. Defining arthritis and measuring functional status in elders: methodological issues in the study of disease and physical disability. *Am J Public Health*, 80, 945-9.
- HALL, J., LASLETT, L., MARTEL-PELLETIER, J., PELLETIER, J. P., ABRAM, F., CICUTTINI, F. & JONES, G. 2012. Change in knee cartilage volume and incident meniscal extrusion as predictors of change in joint space width of the tibiofemoral joint: A five year longitudinal study[abstr]. *Internal Medicine Journal*, 42, 25.
- HANNAN, M. T., FELSON, D. T. & PINCUS, T. 2000. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol*, 27, 1513-7.
- HAUGEN, I. K., BOYESEN, P., SLATKOWSKY-CHRISTENSEN, B., SESSENG, S., VAN DER HEIJDE, D. & KVIEN, T. K. 2012. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis*, 71, 899-904.
- HAWKER, G. A., DAVIS, A. M., FRENCH, M. R., CIBERE, J., JORDAN, J. M., MARCH, L., SUAREZ-ALMAZOR, M., KATZ, J. N. & DIEPPE, P. 2008. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage*, 16, 409-14.
- HAWKER, G. A., GIGNAC, M. A., BADLEY, E., DAVIS, A. M., FRENCH, M. R., LI, Y., PERRUCCIO, A. V., POWER, J. D., SALE, J. & LOU, W. 2011. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res (Hoboken)*, 63, 1382-90.
- HAWKER, G. A., GUAN, J., CROXFORD, R., COYTE, P. C., GLAZIER, R. H., HARVEY, B. J., WRIGHT, J. G., WILLIAMS, J. I. & BADLEY, E. M. 2006. A prospective population-based study of the predictors of undergoing total joint arthroplasty. *Arthritis Rheum*, 54, 3212-20.
- HAWKER, G. A., MIAN, S., KENDZERSKA, T. & FRENCH, M. 2011. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-

- Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)*, 63, S240-52.
- HAWTHORNE, G. & OSBORNE, R. 2005. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. *Aust N Z J Public Health*, 29, 136-42.
- HAWTHORNE, G., RICHARDSON, J., DAY, N. & MCNEIL, H. Using the 'Assessment of Quality of Life' (AQoL) Instrument. 2000. Melbourne:Centre for Health Program Evaluation.
- HEIBERG, T. & KVIEN, T. K. 2002. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum*, 47, 391-7.
- HELIOVAARA, M., MAKELA, M., KNEKT, P., IMPIVAARA, O. & AROMAA, A. 1991. Determinants of sciatica and low-back pain. *Spine (Phila Pa 1976)*, 16, 608-14.
- HILL, C. L., GILL, T. K., MENZ, H. B. & TAYLOR, A. W. 2008. Prevalence and correlates of foot pain in a population-based study: the North West Adelaide health study. *J Foot Ankle Res*, 1, 2.
- HILL, C. L., HUNTER, D. J., NIU, J., CLANCY, M., GUERMAZI, A., GENANT, H., GALE, D., GRAINGER, A., CONAGHAN, P. & FELSON, D. T. 2007. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis*, 66, 1599-603.
- HODGE, A., PATTERSON, A. J., BROWN, W. J., IRELAND, P. & GILES, G. 2000. The Anti Cancer Council of Victoria FFQ: relative validity of nutrient intakes compared with weighed food records in young to middle-aged women in a study of iron supplementation. *Aust N Z J Public Health*, 24, 576-83.
- HOLICK, M. F. 2007. Vitamin D deficiency. *N Engl J Med*, 357, 266-81.
- HONORE, P. & MANTYH, P. W. 2000. Bone cancer pain: from mechanism to model to therapy. *Pain Med*, 1, 303-9.
- HOPMAN-ROCK, M., ODDING, E., HOFMAN, A., KRAAIMAAT, F. W. & BIJLSMA, J. W. 1996. Physical and psychosocial disability in elderly subjects in relation to pain in the hip and/or knee. *J Rheumatol*, 23, 1037-44.
- HSU, Y. H., VENNERS, S. A., TERWEDOW, H. A., FENG, Y., NIU, T., LI, Z., LAIRD, N., BRAIN, J. D., CUMMINGS, S. R., BOUXSEIN, M. L., ROSEN, C. J. & XU, X. 2006. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. *Am J Clin Nutr*, 83, 146-54.
- HUE, O., SIMONEAU, M., MARCOTTE, J., BERRIGAN, F., DORE, J., MARCEAU, P., MARCEAU, S., TREMBLAY, A. & TEASDALE, N. 2007. Body weight is a strong predictor of postural stability. *Gait Posture*, 26, 32-8.

- HUI, M., DOHERTY, M. & ZHANG, W. 2011. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. *Ann Rheum Dis*, 70, 1231-7.
- HUNTER, D. J., GERSTENFELD, L., BISHOP, G., DAVIS, A. D., MASON, Z. D., EINHORN, T. A., MACIEWICZ, R. A., NEWHAM, P., FOSTER, M., JACKSON, S. & MORGAN, E. F. 2009. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. *Arthritis Res Ther*, 11, R11.
- HUNTER, D. J., ZHANG, Y., NIU, J., GOGGINS, J., AMIN, S., LAVALLEY, M. P., GUERMAZI, A., GENANT, H., GALE, D. & FELSON, D. T. 2006. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum*, 54, 1529-35.
- JANKE, E. A., COLLINS, A. & KOZAK, A. T. 2007. Overview of the relationship between pain and obesity: What do we know? Where do we go next? *J Rehabil Res Dev*, 44, 245-62.
- JENSEN, R. K., LEBOEUF-YDE, C., WEDDERKOPP, N., SORENSEN, J. S., JENSEN, T. S. & MANNICHE, C. 2012. Is the development of Modic changes associated with clinical symptoms? A 14-month cohort study with MRI. *Eur Spine J*, 21, 2271-9.
- JENSEN, T. S., KARPPINEN, J., SORENSEN, J. S., NIINIMAKI, J. & LEBOEUF-YDE, C. 2008. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. *Eur Spine J*, 17, 1407-22.
- JOHNELL, O. & KANIS, J. A. 2006. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*, 17, 1726-33.
- JOHNELL, O., O'NEILL, T., FELSENBURG, D., KANIS, J., COOPER, C. & SILMAN, A. J. 1997. Anthropometric measurements and vertebral deformities. European Vertebral Osteoporosis Study (EVOS) Group. *Am J Epidemiol*, 146, 287-93.
- JOKAR, M., MIRFEIZI, Z. & KEYVANPAJOH, K. 2010. The Effect of Alendronate on Symptoms of Knee Osteoarthritis: A Randomized Controlled Trial. *Iran J Med Sci*, 35, 9-15.
- JONES, G. 2008. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr*, 88, 582S-586S.
- JONES, G., COOLEY, H. M. & BELLAMY, N. 2001. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. *Osteoarthritis Cartilage*, 9, 606-11.
- JONES, G., DING, C., SCOTT, F., GLISSON, M. & CICUTTINI, F. 2004. Early radiographic osteoarthritis is associated with substantial changes in

cartilage volume and tibial bone surface area in both males and females. *Osteoarthritis Cartilage*, 12, 169-74.

JONES, G., SCHULTZ, M. G. & DORE, D. 2011. Physical activity and osteoarthritis of the knee: can MRI scans shed more light on this issue? *Phys Sportsmed*, 39, 55-61.

JONES, G., WHITE, C., NGUYEN, T., SAMBROOK, P. N., KELLY, P. J. & EISMAN, J. A. 1996. Prevalent vertebral deformities: relationship to bone mineral density and spinal osteophytosis in elderly men and women. *Osteoporos Int*, 6, 233-9.

JONES, G., WHITE, C., SAMBROOK, P. & EISMAN, J. 1998. Allelic variation in the vitamin D receptor, lifestyle factors and lumbar spinal degenerative disease. *Ann Rheum Dis*, 57, 94-9.

JORDAN, J., LUTA, G., RENNER, J., DRAGOMIR, A., HOCHBERG, M. & FRYER, J. 1997. Knee pain and knee osteoarthritis severity in self-reported task specific disability: the Johnston County Osteoarthritis Project. *J Rheumatol*, 24, 1344-9.

JORDE, R., SNEVE, M., HUTCHINSON, M., EMAUS, N., FIGENSCHAU, Y. & GRIMNES, G. 2010. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. *Am J Epidemiol*, 171, 903-8.

JUHAKOSKI, R., TENHONEN, S., ANTTONEN, T., KAUPPINEN, T. & AROKOSKI, J. P. 2008. Factors affecting self-reported pain and physical function in patients with hip osteoarthritis. *Arch Phys Med Rehabil*, 89, 1066-73.

JÜNI, P., DIEPPE, P., DONOVAN, J., PETERS, T., EACHUS, J., PEARSON, N., GREENWOOD, R. & FRANKEL, S. 2003. Population requirement for primary knee replacement surgery: a cross-sectional study. *Rheumatology (Oxford)*, 42, 516-21.

KAMALERI, Y., NATVIG, B., IHLEBAEK, C. M., BENTH, J. S. & BRUUSGAARD, D. 2008. Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. *Eur J Pain*, 12, 742-8.

KATZ, J. D. & SHAH, T. 2009. Persistent pain in the older adult: what should we do now in light of the 2009 American geriatrics society clinical practice guideline? *Pol Arch Med Wewn*, 119, 795-800.

KAWASAKI, T., KUROSAWA, H., IKEDA, H., KIM, S. G., OSAWA, A., TAKAZAWA, Y., KUBOTA, M. & ISHIJIMA, M. 2008. Additive effects of glucosamine or risedronate for the treatment of osteoarthritis of the knee combined with home exercise: a prospective randomized 18-month trial. *J Bone Miner Metab*, 26, 279-87.

KEEFE, F. J., LEFEBVRE, J. C., EGERT, J. R., AFFLECK, G., SULLIVAN, M. J. & CALDWELL, D. S. 2000. The relationship of gender to pain, pain

behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain*, 87, 325-34.

KEEFE, F. J. & SOMERS, T. J. 2010. Psychological approaches to understanding and treating arthritis pain. *Nat Rev Rheumatol*, 6, 210-6.

KEEN, H. I., WAKEFIELD, R. J., GRAINGER, A. J., HENSOR, E. M., EMERY, P. & CONAGHAN, P. G. 2008. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum*, 59, 1756-63.

KEENAN, A. M., TENNANT, A., FEAR, J., EMERY, P. & CONAGHAN, P. G. 2006. Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. *Arthritis Rheum*, 55, 757-64.

KELLGREN, J. H. & LAWRENCE, J. S. 1957. Radiological assessment of osteo-arthritis. *Ann Rheum Dis*, 16, 494-502.

KIDD, B. L., MORRIS, V. H. & URBAN, L. 1996. Pathophysiology of joint pain. *Ann Rheum Dis*, 55, 276-83.

KIM, I., KIM, H. A., SEO, Y. I., SONG, Y. W., HUNTER, D. J., JEONG, J. Y. & KIM, D. H. 2010. Tibiofemoral osteoarthritis affects quality of life and function in elderly Koreans, with women more adversely affected than men. *BMC Musculoskelet Disord*, 11, 129.

KIM, K. C., SHIN, D. H., LEE, S. Y., IM, J. A. & LEE, D. C. 2010. Relation between obesity and bone mineral density and vertebral fractures in Korean postmenopausal women. *Yonsei Med J*, 51, 857-63.

KOLL, R., BUHR, M., DIETER, R., PABST, H., PREDEL, H. G., PETROWICZ, O., GIANNETTI, B., KLINGENBURG, S. & STAIGER, C. 2004. Efficacy and tolerance of a comfrey root extract (Extr. Rad. Symphyti) in the treatment of ankle distortions: results of a multicenter, randomized, placebo-controlled, double-blind study. *Phytomedicine*, 11, 470-7.

KOLL, R. & KLINGENBURG, S. 2002. [Therapeutic characteristance and tolerance of topical comfrey preparations. Results of an observational study of patients]. *Fortschr Med Orig*, 120, 1-9.

KOO, K. H., AHN, I. O., KIM, R., SONG, H. R., JEONG, S. T., NA, J. B., KIM, Y. S. & CHO, S. H. 1999. Bone marrow edema and associated pain in early stage osteonecrosis of the femoral head: prospective study with serial MR images. *Radiology*, 213, 715-22.

KORNAAT, P. R., KLOPPENBURG, M., SHARMA, R., BOTHA-SCHEEPERS, S. A., LE GRAVERAND, M. P., COENE, L. N., BLOEM, J. L. & WATT, I. 2007. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol*, 17, 3073-8.

KULKARNI, B., BENTLEY, D. E., ELLIOTT, R., JULYAN, P. J., BOGER, E., WATSON, A., BOYLE, Y., EL-DEREDY, W. & JONES, A. K. 2007. Arthritic

pain is processed in brain areas concerned with emotions and fear. *Arthritis Rheum*, 56, 1345-54.

KUMAR, S. 2004. *Muscle strength*, Florida, USA, CRC Press.

LANE, N. E., BRANDT, K., HAWKER, G., PEEVA, E., SCHREYER, E., TSUJI, W. & HOCHBERG, M. C. 2011. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage*, 19, 478-82.

LANE, N. E., GORE, L. R., CUMMINGS, S. R., HOCHBERG, M. C., SCOTT, J. C., WILLIAMS, E. N. & NEVITT, M. C. 1999. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum*, 42, 854-60.

LANGFORD, R., MCKENNA, F., RATCLIFFE, S., VOJTASSAK, J. & RICHARZ, U. 2006. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. *Arthritis Rheum*, 54, 1829-37.

LAVALLEY, M., MCALINDON, T. E., EVANS, S., CHAISSON, C. E. & FELSON, D. T. 2001. Problems in the development and validation of questionnaire-based screening instruments for ascertaining cases with symptomatic knee osteoarthritis: the Framingham Study. *Arthritis Rheum*, 44, 1105-13.

LEBOEUF-YDE, C. 2000. Body weight and low back pain. A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976)*, 25, 226-37.

LEE, P. & CHEN, R. 2008. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Arch Intern Med*, 168, 771-2.

LEVANON, D. & STEIN, H. 1995. Quantitative analysis of chondroitin sulphate retention by tannic acid during preparation of specimens for electron microscopy. *Histochem J*, 27, 457-65.

LIBICHER, M., IVANCIC, M., HOFFMANN, M. & WENZ, W. 2005. Early changes in experimental osteoarthritis using the Pond-Nuki dog model: technical procedure and initial results of in vivo MR imaging. *Eur Radiol*, 15, 390-4.

LIPS, P. 2001. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev*, 22, 477-501.

LIPS, P. 2004. Which circulating level of 25-hydroxyvitamin D is appropriate? *J Steroid Biochem Mol Biol*, 89-90, 611-4.

LIPS, P. 2006. Vitamin D physiology. *Prog Biophys Mol Biol*, 92, 4-8.

LIPS, P., VAN SCHOOR, N. M. & BRAVENBOER, N. 2008. Vitamin D-Related Disorders. In: ROSEN, C. J., COMPSTON, J. E. & LIAN, J. B. (eds.) *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 7th ed. Washington, D.C.: American Society for Bone and Mineral Research.

LOESER, R. F., GOLDRING, S. R., SCANZELLO, C. R. & GOLDRING, M. B. 2012. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum*, 64, 1697-707.

LORD, S. R., ROGERS, M. W., HOWLAND, A. & FITZPATRICK, R. 1999. Lateral stability, sensorimotor function and falls in older people. *J Am Geriatr Soc*, 47, 1077-81.

LYRITIS, G. P., MAYASIS, B., TSAKALAKOS, N., LAMBROPOULOS, A., GAZI, S., KARACHALIOS, T., TSEKOURA, M. & YIATZIDES, A. 1989. The natural history of the osteoporotic vertebral fracture. *Clin Rheumatol*, 8, 66-9.

MAZZUCA, S. A., BRANDT, K. D., SCHAUWECKER, D. S., KATZ, B. P., MEYER, J. M., LANE, K. A., BRADLEY, J. D., HUGENBERG, S. T., WOLFE, F., MORELAND, L. W., HECK, L. W., YOCUM, D. E., SCHNITZER, T. J., SHARMA, L., MANZI, S. & ODDIS, C. V. 2005. Severity of joint pain and Kellgren-Lawrence grade at baseline are better predictors of joint space narrowing than bone scintigraphy in obese women with knee osteoarthritis. *J Rheumatol*, 32, 1540-6.

MCALINDON, T. & DIEPPE, P. 1989. Osteoarthritis: definitions and criteria. *Ann Rheum Dis*, 48, 531-2.

MCALINDON, T. E., COOPER, C., KIRWAN, J. R. & DIEPPE, P. A. 1993. Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis*, 52, 258-62.

MCALINDON, T. E., JACQUES, P., ZHANG, Y., HANNAN, M. T., ALIABADI, P., WEISSMAN, B., RUSH, D., LEVY, D. & FELSON, D. T. 1996. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum*, 39, 648-56.

MCBETH, J., PYE, S. R., O'NEILL, T. W., MACFARLANE, G. J., TAJAR, A., BARTFAI, G., BOONEN, S., BOUILLON, R., CASANUEVA, F., FINN, J. D., FORTI, G., GIWERCMAN, A., HAN, T. S., HUHTANIEMI, I. T., KULA, K., LEAN, M. E., PENDLETON, N., PUNAB, M., SILMAN, A. J., VANDERSCHUEREN, D. & WU, F. C. 2010. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. *Ann Rheum Dis*, 69, 1448-52.

MCCONNELL, S., KOLOPACK, P. & DAVIS, A. M. 2001. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Care Res (Hoboken)*, 45, 453-61.

MEIZER, R., MERANER, D., MEIZER, E., RADDA, C., LANDSIEDL, F. & AIGNER, N. 2009. Outcome of painful bone marrow edema of the femoral head following treatment with parenteral iloprost. *Indian J Orthop*, 43, 36-9.

MEIZER, R., RADDA, C., STOLZ, G., KOTSARIS, S., PETJE, G., KRASNY, C., WLK, M., MAYERHOFER, M., LANDSIEDL, F. & AIGNER, N. 2005. MRI-controlled analysis of 104 patients with painful bone marrow edema in

different joint localizations treated with the prostacyclin analogue iloprost. *Wien Klin Wochenschr*, 117, 278-86.

MELIN, A., WILSKES, J., RINGERTZ, H. & SAAF, M. 2001. Seasonal variations in serum levels of 25-hydroxyvitamin D and parathyroid hormone but no detectable change in femoral neck bone density in an older population with regular outdoor exposure. *J Am Geriatr Soc*, 49, 1190-6.

MICHEL, A., KOHLMANN, T. & RASPE, H. 1997. The association between clinical findings on physical examination and self-reported severity in back pain. Results of a population-based study. *Spine (Phila Pa 1976)*, 22, 296-303; discussion 303-4.

MIMS AUSTRALIA 2009. *MIMS annual*, CMPMedica, St Leonards.

MNATZAGANIAN, G., RYAN, P., NORMAN, P. E., DAVIDSON, D. C. & HILLER, J. E. 2011. Smoking, body weight, physical exercise, and risk of lower limb total joint replacement in a population-based cohort of men. *Arthritis Rheum*, 63, 2523-30.

MODIC, M. T., STEINBERG, P. M., ROSS, J. S., MASARYK, T. J. & CARTER, J. R. 1988. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*, 166, 193-9.

MURAKI, S., DENNISON, E., JAMESON, K., BOUCHER, B. J., AKUNE, T., YOSHIMURA, N., JUDGE, A., ARDEN, N. K., JAVAID, K. & COOPER, C. 2011. Association of vitamin D status with knee pain and radiographic knee osteoarthritis. *Osteoarthritis Cartilage*, 19, 1301-6.

MURAKI, S., OKA, H., AKUNE, T., EN-YO, Y., YOSHIDA, M., SUZUKI, T., YOSHIDA, H., ISHIBASHI, H., TOKIMURA, F., YAMAMOTO, S., NAKAMURA, K., KAWAGUCHI, H. & YOSHIMURA, N. 2011. Independent association of joint space narrowing and osteophyte formation at the knee with health-related quality of life in Japan: a cross-sectional study. *Arthritis Rheum*, 63, 3859-64.

NELLEN, J. F., SMULDERS, Y. M., JOS FRISSEN, P. H., SLAATS, E. H. & SILBERBUSCH, J. 1996. Hypovitaminosis D in immigrant women: slow to be diagnosed. *BMJ*, 312, 570-2.

NEOGI, T., NEVITT, M. C., ENSRUD, K. E., BAUER, D. & FELSON, D. T. 2008. The effect of alendronate on progression of spinal osteophytes and disc-space narrowing. *Ann Rheum Dis*, 67, 1427-30.

NEWMAN, A. B., KUPELIAN, V., VISSER, M., SIMONSICK, E. M., GOODPASTER, B. H., KRITCHEVSKY, S. B., TYLAVSKY, F. A., RUBIN, S. M. & HARRIS, T. B. 2006. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*, 61, 72-7.

NIELSON, C. M., MARSHALL, L. M., ADAMS, A. L., LEBLANC, E. S., CAWTHON, P. M., ENSRUD, K., STEFANICK, M. L., BARRETT-CONNOR,

E. & ORWOLL, E. S. 2011. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). *J Bone Miner Res*, 26, 496-502.

NORIMATSU, T., OSAKI, M., TOMITA, M., YE, Z., ABE, Y., HONDA, S., KANAGAE, M., MIZUKAMI, S., TAKAMURA, N., KUSANO, Y., SHINDO, H. & AOYAGI, K. 2011. Factors predicting health-related quality of life in knee osteoarthritis among community-dwelling women in Japan: the Hizen-Oshima study. *Orthopedics*, 34, e535-40.

OOMS, M. E. 1994. *Osteoporosis in elderly women; vitamin D deficiency and other risk factors*. PhD, Vrije Universiteit.

OSBORNE, R. H., HAWTHORNE, G., LEW, E. A. & GRAY, L. C. 2003. Quality of life assessment in the community-dwelling elderly: validation of the Assessment of Quality of Life (AQoL) Instrument and comparison with the SF-36. *J Clin Epidemiol*, 56, 138-47.

OSTERGAARD, M., STOLTENBERG, M., GIDEON, P., SORENSEN, K., HENRIKSEN, O. & LORENZEN, I. 1996. Changes in synovial membrane and joint effusion volumes after intraarticular methylprednisolone. Quantitative assessment of inflammatory and destructive changes in arthritis by MRI. *J Rheumatol*, 23, 1151-61.

OSUNKWO, I., ZIEGLER, T. R., ALVAREZ, J., MCCRACKEN, C., CHERRY, K., OSUNKWO, C. E., OFORI-ACQUAH, S. F., GHOSH, S., OGUNBOBODE, A., RHODES, J., ECKMAN, J. R., DAMPIER, C. & TANGPRICHA, V. 2012. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. *Br J Haematol*, 159, 211-5.

OWUSU, W., WILLETT, W., ASCHERIO, A., SPIEGELMAN, D., RIMM, E., FESKANICH, D. & COLDITZ, G. 1998. Body anthropometry and the risk of hip and wrist fractures in men: results from a prospective study. *Obes Res*, 6, 12-9.

PARKS, E. L., GEHA, P. Y., BALIKI, M. N., KATZ, J., SCHNITZER, T. J. & APKARIAN, A. V. 2011. Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. *Eur J Pain*, 15, 843 e1-14.

PEAT, G., MCCARNEY, R. & CROFT, P. 2001. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis*, 60, 91-7.

PELLETIER, J. P., RAYNAULD, J. P., BERTHIAUME, M. J., ABRAM, F., CHOQUETTE, D., HARAOU, B., BEARY, J. F., CLINE, G. A., MEYER, J. M. & MARTEL-PELLETIER, J. 2007. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. *Arthritis Res Ther*, 9, R74.

PEPE, J., ROMAGNOLI, E., NOFRONI, I., PACITTI, M. T., DE GERONIMO, S., LETIZIA, C., TONNARINI, G., SCARPIELLO, A., D'ERASMO, E. & MINISOLA, S. 2005. Vitamin D status as the major factor determining the

circulating levels of parathyroid hormone: a study in normal subjects. *Osteoporos Int*, 16, 805-12.

PEREIRA, D., PELETEIRO, B., ARAUJO, J., BRANCO, J., SANTOS, R. A. & RAMOS, E. 2011. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage*, 19, 1270-85.

PETERLIK, M. & CROSS, H. S. 2005. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest*, 35, 290-304.

PHAM, T., VAN DER HEIJDE, D., ALTMAN, R. D., ANDERSON, J. J., BELLAMY, N., HOCHBERG, M., SIMON, L., STRAND, V., WOODWORTH, T. & DOUGADOS, M. 2004. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage*, 12, 389-99.

PICAVET, H. S. & SCHOUTEN, J. S. 2003. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. *Pain*, 102, 167-78.

PINCUS, T., BURTON, A. K., VOGEL, S. & FIELD, A. P. 2002. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine (Phila Pa 1976)*, 27, E109-20.

PIRRO, M., FABBRICIANI, G., LELI, C., CALLARELLI, L., MANFREDELLI, M. R., FIORONI, C., MANNARINO, M. R., SCARPONI, A. M. & MANNARINO, E. 2010. High weight or body mass index increase the risk of vertebral fractures in postmenopausal osteoporotic women. *J Bone Miner Metab*, 28, 88-93.

PLOTNIKOFF, G. A. & QUIGLEY, J. M. 2003. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*, 78, 1463-70.

POLIT, D. F. & GILLESPIE, B. M. 2010. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health*, 33, 355-68.

POLLINTINE, P., LUO, J., OFFA-JONES, B., DOLAN, P. & ADAMS, M. A. 2009. Bone creep can cause progressive vertebral deformity. *Bone*, 45, 466-72.

PONGCHAIYAKUL, C., NGUYEN, N. D., JONES, G., CENTER, J. R., EISMAN, J. A. & NGUYEN, T. V. 2005. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. *J Bone Miner Res*, 20, 1349-55.

POULIOT, M. C., DESPRES, J. P., LEMIEUX, S., MOORJANI, S., BOUCHARD, C., TREMBLAY, A., NADEAU, A. & LUPIEN, P. J. 1994. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol*, 73, 460-8.

- PRABHALA, A., GARG, R. & DANDONA, P. 2000. Severe myopathy associated with vitamin D deficiency in western New York. *Arch Intern Med*, 160, 1199-203.
- PREDEL, H. G., GIANNETTI, B., KOLL, R., BULITTA, M. & STAIGER, C. 2005. Efficacy of a comfrey root extract ointment in comparison to a diclofenac gel in the treatment of ankle distortions: results of an observer-blind, randomized, multicenter study. *Phytomedicine*, 12, 707-14.
- PREMAOR, M. O., PILBROW, L., TONKIN, C., PARKER, R. A. & COMPSTON, J. 2010. Obesity and fractures in postmenopausal women. *J Bone Miner Res*, 25, 292-7.
- RAYNAULD, J. P., BUCKLAND-WRIGHT, C., WARD, R., CHOQUETTE, D., HARAOU, B., MARTEL-PELLETIER, J., UTHMAN, I., KHY, V., TREMBLAY, J. L., BERTRAND, C. & PELLETIER, J. P. 2003. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*, 48, 370-7.
- RAYNAULD, J. P., MARTEL-PELLETIER, J., BERTHIAUME, M. J., ABRAM, F., CHOQUETTE, D., HARAOU, B., BEARY, J. F., CLINE, G. A., MEYER, J. M. & PELLETIER, J. P. 2008. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann Rheum Dis*, 67, 683-8.
- RAYNAULD, J. P., MARTEL-PELLETIER, J., BERTHIAUME, M. J., LABONTE, F., BEAUDOIN, G., DE GUISE, J. A., BLOCH, D. A., CHOQUETTE, D., HARAOU, B., ALTMAN, R. D., HOCHBERG, M. C., MEYER, J. M., CLINE, G. A. & PELLETIER, J. P. 2004. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum*, 50, 476-87.
- RAYNAULD, J. P., MARTEL-PELLETIER, J., HARAOU, B., CHOQUETTE, D., DORAIS, M., WILDI, L. M., ABRAM, F. & PELLETIER, J. P. 2011. Risk factors predictive of joint replacement in a 2-year multicentre clinical trial in knee osteoarthritis using MRI: results from over 6 years of observation. *Ann Rheum Dis*, 70, 1382-8.
- REGAN, E. A., BOWLER, R. P. & CRAPO, J. D. 2008. Joint fluid antioxidants are decreased in osteoarthritic joints compared to joints with macroscopically intact cartilage and subacute injury. *Osteoarthritis Cartilage*, 16, 515-21.
- REGINATO, A. J., FALASCA, G. F., PAPPU, R., MCKNIGHT, B. & AGHA, A. 1999. Musculoskeletal manifestations of osteomalacia: report of 26 cases and literature review. *Semin Arthritis Rheum*, 28, 287-304.
- REGINSTER, J. Y., BADURSKI, J., BELLAMY, N., BENSON, W., CHAPURLAT, R., CHEVALIER, X., CHRISTIANSEN, C., GENANT, H., NAVARRO, F., NASONOV, E., SAMBROOK, P. N., SPECTOR, T. D. & COOPER, C. 2012. Efficacy and safety of strontium ranelate in the treatment

of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann Rheum Dis*.

REID, D. M., DEVOGELAER, J. P., SAAG, K., ROUX, C., LAU, C. S., REGINSTER, J. Y., PAPANASTASIOU, P., FERREIRA, A., HARTL, F., FASHOLA, T., MESENBRINK, P. & SAMBROOK, P. N. 2009. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*, 373, 1253-63.

REID, I. R. 2008. Relationships between fat and bone. *Osteoporos Int*, 19, 595-606.

REID, I. R., GAMBLE, G. D., MESENBRINK, P., LAKATOS, P. & BLACK, D. M. 2010. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab*, 95, 4380-7.

REZAI, M., COTE, P., CASSIDY, J. D. & CARROLL, L. 2009. The association between prevalent neck pain and health-related quality of life: a cross-sectional analysis. *Eur Spine J*, 18, 371-81.

RIDDLE, D. L., KONG, X. & FITZGERALD, G. K. 2011. Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*, 19, 1095-101.

RINGE, J. D. & BODY, J. J. 2007. A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover. *Clin Exp Rheumatol*, 25, 766-74.

ROBINSON, D. R., TASHJIAN, A. H., JR. & LEVINE, L. 1975. Prostaglandin-stimulated bone resorption by rheumatoid synovia. A possible mechanism for bone destruction in rheumatoid arthritis. *J Clin Invest*, 56, 1181-8.

ROELOFS, A. J., THOMPSON, K., EBETINO, F. H., ROGERS, M. J. & COXON, F. P. 2010. Bisphosphonates: molecular mechanisms of action and effects on bone cells, monocytes and macrophages. *Current Pharmaceutical Design*, 16, 2950-60.

ROEMER, F. W., GUERMAZI, A., JAVAID, M. K., LYNCH, J. A., NIU, J., ZHANG, Y., FELSON, D. T., LEWIS, C. E., TORNER, J. & NEVITT, M. C. 2009. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann Rheum Dis*, 68, 1461-5.

ROEMER, F. W., HUNTER, D. J., WINTERSTEIN, A., LI, L., KIM, Y. J., CIBERE, J., MAMISCH, T. C. & GUERMAZI, A. 2011. Hip Osteoarthritis MRI Scoring System (HOAMS): reliability and associations with radiographic and clinical findings. *Osteoarthritis Cartilage*, 19, 946-62.

ROGERS, M. J. 2003. New insights into the molecular mechanisms of action of bisphosphonates. *Curr Pharm Des*, 9, 2643-58.

ROOS, E. M., ROOS, H. P., LOHMANDER, L. S., EKDAHL, C. & BEYNNON, B. D. 1998. Knee Injury and Osteoarthritis Outcome Score (KOOS)--

development of a self-administered outcome measure. *J Orthop Sports Phys Ther*, 28, 88-96.

ROSS, P. D. 1997. Clinical consequences of vertebral fractures. *Am J Med*, 103, 30S-42S; discussion 42S-43S.

ROSS, P. D., DAVIS, J. W., EPSTEIN, R. S. & WASNICH, R. D. 1991. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med*, 114, 919-23.

ROSS, P. D., HUANG, C., KARPf, D., LYDICK, E., COEL, M., HIRSCH, L. & WASNICH, R. D. 1996. Blinded reading of radiographs increases the frequency of errors in vertebral fracture detection. *J Bone Miner Res*, 11, 1793-800.

ROSSINI, M., VIAPIANA, O., RAMONDA, R., BIANCHI, G., OLIVIERI, I., LAPADULA, G. & ADAMI, S. 2009. Intra-articular clodronate for the treatment of knee osteoarthritis: dose ranging study vs hyaluronic acid. *Rheumatology (Oxford)*, 48, 773-8.

ROUX, C., FECHTENBAUM, J., KOLTA, S., BRIOT, K. & GIRARD, M. 2007. Mild prevalent and incident vertebral fractures are risk factors for new fractures. *Osteoporos Int*, 18, 1617-24.

SANDERS, K. M., STUART, A. L., WILLIAMSON, E. J., SIMPSON, J. A., KOTOWICZ, M. A., YOUNG, D. & NICHOLSON, G. C. 2010. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*, 303, 1815-22.

SAUNDERS, J., DING, C., CICUTTINI, F. & JONES, G. 2011. Radiographic osteoarthritis and pain are independent predictors of knee cartilage loss: a prospective study. *Intern Med J*.

SAVIOLA, G., ABDI-ALI, L., CAMPOSTRINI, L., SACCO, S., BAIARDI, P., MANFREDI, M., MANNONI, A. & BENUCCI, M. 2012. Clodronate and hydroxychloroquine in erosive osteoarthritis: a 24-month open randomized pilot study. *Mod Rheumatol*, 22, 256-63.

SCHAIBLE, H. G. & GRUBB, B. D. 1993. Afferent and spinal mechanisms of joint pain. *Pain*, 55, 5-54.

SCOTT, D., BLIZZARD, L., FELL, J., DING, C., WINZENBERG, T. & JONES, G. 2010. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. *Clin Endocrinol (Oxf)*, 73, 581-7.

SCOTT, D., BLIZZARD, L., FELL, J. & JONES, G. 2009. Ambulatory activity, body composition, and lower-limb muscle strength in older adults. *Med Sci Sports Exerc*, 41, 383-9.

SCOTT, D., BLIZZARD, L., FELL, J. & JONES, G. 2009. Statin therapy, muscle function and falls risk in community-dwelling older adults. *QJM*, 102, 625-33.

- SCOTT, D., BLIZZARD, L., FELL, J. & JONES, G. 2010. Prospective associations between ambulatory activity, body composition and muscle function in older adults. *Scand J Med Sci Sports*, 21, e168-75.
- SERHAN, E., NEWTON, P., ALI, H. A., WALFORD, S. & SINGH, B. M. 1999. Prevalence of hypovitaminosis D in Indo-Asian patients attending a rheumatology clinic. *Bone*, 25, 609-11.
- SINGH, J. A., NELSON, D. B., FINK, H. A. & NICHOL, K. L. 2005. Health-related quality of life predicts future health care utilization and mortality in veterans with self-reported physician-diagnosed arthritis: the veterans arthritis quality of life study. *Semin Arthritis Rheum*, 34, 755-65.
- SKAGGS, D. L., LORO, M. L., PITUKCHEEWANONT, P., TOLO, V. & GILSANZ, V. 2001. Increased body weight and decreased radial cross-sectional dimensions in girls with forearm fractures. *J Bone Miner Res*, 16, 1337-42.
- SMITH, D. B. & JACOBSON, B. H. 2011. Effect of a blend of comfrey root extract (*Symphytum officinale* L.) and tannic acid creams in the treatment of osteoarthritis of the knee: randomized, placebo-controlled, double-blind, multiclinical trials. *J Chiropr Med*, 10, 147-56.
- SMITH, H., ANDERSON, F., RAPHAEL, H., MASLIN, P., CROZIER, S. & COOPER, C. 2007. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology (Oxford)*, 46, 1852-7.
- SMITH, M. D., WETHERALL, M., DARBY, T., ESTERMAN, A., SLAVOTINEK, J., ROBERTS-THOMSON, P., COLEMAN, M. & AHERN, M. J. 2003. A randomized placebo-controlled trial of arthroscopic lavage versus lavage plus intra-articular corticosteroids in the management of symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)*, 42, 1477-85.
- SOLOMON, S. D., MCMURRAY, J. J., PFEFFER, M. A., WITTES, J., FOWLER, R., FINN, P., ANDERSON, W. F., ZAUBER, A., HAWK, E. & BERTAGNOLLI, M. 2005. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*, 352, 1071-80.
- SOWERS, M. F., KSHIRSAGAR, A., CRUTCHFIELD, M. M. & UPDIKE, S. 1992. Joint influence of fat and lean body composition compartments on femoral bone mineral density in premenopausal women. *Am J Epidemiol*, 136, 257-65.
- SPECTOR, T. D., CONAGHAN, P. G., BUCKLAND-WRIGHT, J. C., GARNERO, P., CLINE, G. A., BEARY, J. F., VALENT, D. J. & MEYER, J. M. 2005. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. *Arthritis Res Ther*, 7, R625-33.
- SPEER, K. P., SPRITZER, C. E., BASSETT, F. H., 3RD, FEAGIN, J. A., JR. & GARRETT, W. E., JR. 1992. Osseous injury associated with acute tears of the anterior cruciate ligament. *Am J Sports Med*, 20, 382-9.

- STANNUS, O. P., JONES, G., BLIZZARD, L., CICUTTINI, F. M. & DING, C. 2013. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. *Ann Rheum Dis*, 72, 535-40.
- STICKEL, F. & SEITZ, H. K. 2000. The efficacy and safety of comfrey. *Public Health Nutr*, 3, 501-8.
- STRAUBE, S., DERRY, S., MOORE, R. A. & MCQUAY, H. J. 2010. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev*, CD007771.
- SULLIVAN, M. J., THORN, B., HAYTHORNTHWAITE, J. A., KEEFE, F., MARTIN, M., BRADLEY, L. A. & LEFEBVRE, J. C. 2001. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain*, 17, 52-64.
- SUMMERS, M. N., HALEY, W. E., REVEILLE, J. D. & ALARCON, G. S. 1988. Radiographic assessment and psychologic variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. *Arthritis Rheum*, 31, 204-9.
- TALJANOVIC, M. S., GRAHAM, A. R., BENJAMIN, J. B., GMITRO, A. F., KRUPINSKI, E. A., SCHWARTZ, S. A., HUNTER, T. B. & RESNICK, D. L. 2008. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. *Skeletal Radiol*, 37, 423-31.
- TANAMAS, S. K., WLUKA, A. E., PELLETIER, J. P., PELLETIER, J. M., ABRAM, F., BERRY, P. A., WANG, Y., JONES, G. & CICUTTINI, F. M. 2010. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. *Rheumatology (Oxford)*, 49, 2413-9.
- THOMAS, E., PEAT, G., HARRIS, L., WILKIE, R. & CROFT, P. R. 2004. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain*, 110, 361-8.
- THUMBOO, J., CHEW, L. H. & LEWIN-KOH, S. C. 2002. Socioeconomic and psychosocial factors influence pain or physical function in Asian patients with knee or hip osteoarthritis. *Ann Rheum Dis*, 61, 1017-20.
- URQUHART, D. M., BERRY, P., WLUKA, A. E., STRAUSS, B. J., WANG, Y., PROIETTO, J., JONES, G., DIXON, J. B. & CICUTTINI, F. M. 2011. 2011 Young Investigator Award winner: Increased fat mass is associated with high levels of low back pain intensity and disability. *Spine (Phila Pa 1976)*, 36, 1320-5.
- URWIN, M., SYMMONS, D., ALLISON, T., BRAMMAH, T., BUSBY, H., ROXBY, M., SIMMONS, A. & WILLIAMS, G. 1998. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of

symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis*, 57, 649-55.

VALDES, A. M., DE WILDE, G., DOHERTY, S. A., LORIES, R. J., VAUGHN, F. L., LASLETT, L. L., MACIEWICZ, R. A., SONI, A., HART, D. J., ZHANG, W., MUIR, K. R., DENNISON, E. M., WHEELER, M., LEAVERTON, P., COOPER, C., SPECTOR, T. D., CICUTTINI, F. M., CHAPMAN, V., JONES, G., ARDEN, N. K. & DOHERTY, M. 2011. The Ile585Val TRPV1 variant is involved in risk of painful knee osteoarthritis. *Ann Rheum Dis*, 70, 1556-61.

VAN BAAR, M. E., DEKKER, J., LEMMENS, J. A., OOSTENDORP, R. A. & BIJLSMA, J. W. 1998. Pain and disability in patients with osteoarthritis of hip or knee: the relationship with articular, kinesiological, and psychological characteristics. *J Rheumatol*, 25, 125-33.

VAN DER MEI, I. A., DORE, D., WINZENBERG, T., BLIZZARD, L. & JONES, G. 2012. Vitamin D deficiency in Tasmania: a whole of life perspective. *Intern Med J*, 42, 1137-44.

WALLS, H. L., WOLFE, R., HABY, M. M., MAGLIANO, D. J., DE COURTEN, M., REID, C. M., MCNEIL, J. J., SHAW, J. & PEETERS, A. 2010. Trends in BMI of urban Australian adults, 1980-2000. *Public Health Nutr*, 13, 631-8.

WALSH, D. A. & CHAPMAN, V. 2011. Bisphosphonates for osteoarthritis. *Arthritis Res Ther*, 13, 128.

WALSH, D. A., MCWILLIAMS, D. F., TURLEY, M. J., DIXON, M. R., FRANCES, R. E., MAPP, P. I. & WILSON, D. 2010. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology (Oxford)*, 49, 1852-61.

WARNER, A. E. & ARNSPIGER, S. A. 2008. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol*, 14, 12-6.

WEBB, R., BRAMMAH, T., LUNT, M., URWIN, M., ALLISON, T. & SYMMONS, D. 2003. Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. *Spine (Phila Pa 1976)*, 28, 1195-202.

WILDI, L. M., RAYNAULD, J. P., MARTEL-PELLETIER, J., BEAULIEU, A., BESSETTE, L., MORIN, F., ABRAM, F., DORAIS, M. & PELLETIER, J. P. 2011. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis*, 70, 982-9.

WLUKA, A. E., WANG, Y., DAVIES-TUCK, M., ENGLISH, D. R., GILES, G. G. & CICUTTINI, F. M. 2008. Bone marrow lesions predict progression of cartilage defects and loss of cartilage volume in healthy middle-aged adults without knee pain over 2 yrs. *Rheumatology (Oxford)*, 47, 1392-6.

- WOJTYS, E. M., BEAMAN, D. N., GLOVER, R. A. & JANDA, D. 1990. Innervation of the human knee joint by substance-P fibers. *Arthroscopy*, 6, 254-63.
- WOO, J., LEUNG, J. & LAU, E. 2009. Prevalence and correlates of musculoskeletal pain in Chinese elderly and the impact on 4-year physical function and quality of life. *Public Health*, 123, 549-56.
- YONEDA, T., HATA, K., NAKANISHI, M., NAGAE, M., NAGAYAMA, T., WAKABAYASHI, H., NISHISHO, T., SAKURAI, T. & HIRAGA, T. 2011. Involvement of acidic microenvironment in the pathophysiology of cancer-associated bone pain. *Bone*, 48, 100-5.
- YUDOH, K., NAKAMURA, H., MASUKO-HONGO, K., KATO, T. & NISHIOKA, K. 2005. Catabolic stress induces expression of hypoxia-inducible factor (HIF)-1 alpha in articular chondrocytes: involvement of HIF-1 alpha in the pathogenesis of osteoarthritis. *Arthritis Res Ther*, 7, R904-14.
- ZANETTI, M., BRUDER, E., ROMERO, J. & HODLER, J. 2000. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology*, 215, 835-40.
- ZANINOTTO, P., HEAD, J., STAMATAKIS, E., WARDLE, H. & MINDELL, J. 2009. Trends in obesity among adults in England from 1993 to 2004 by age and social class and projections of prevalence to 2012. *J Epidemiol Community Health*, 63, 140-6.
- ZENG, Q. Y., CHEN, R., XIAO, Z. Y., HUANG, S. B., LIU, Y., XU, J. C., CHEN, S. L., DARMAWAN, J., COUCHMAN, K. G., WIGLEY, R. D. & MUIRDEN, K. D. 2004. Low prevalence of knee and back pain in southeast China; the Shantou COPCORD study. *J Rheumatol*, 31, 2439-43.
- ZHAI, G., BLIZZARD, L., SRIKANTH, V., DING, C., COOLEY, H., CICUTTINI, F. & JONES, G. 2006. Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. *Arthritis Rheum*, 55, 264-71.
- ZHANG, W., MOSKOWITZ, R. W., NUKI, G., ABRAMSON, S., ALTMAN, R. D., ARDEN, N., BIERMA-ZEINSTRAS, S., BRANDT, K. D., CROFT, P., DOHERTY, M., DOUGADOS, M., HOCHBERG, M., HUNTER, D. J., KWOH, K., LOHMANDER, L. S. & TUGWELL, P. 2008. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*, 16, 137-62.
- ZHANG, W., NUKI, G., MOSKOWITZ, R. W., ABRAMSON, S., ALTMAN, R. D., ARDEN, N. K., BIERMA-ZEINSTRAS, S., BRANDT, K. D., CROFT, P., DOHERTY, M., DOUGADOS, M., HOCHBERG, M., HUNTER, D. J., KWOH, K., LOHMANDER, L. S. & TUGWELL, P. 2010. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*, 18, 476-99.

- ZHANG, W., ROBERTSON, J., JONES, A. C., DIEPPE, P. A. & DOHERTY, M. 2008. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis*, 67, 1716-23.
- ZHANG, Y., NEVITT, M., NIU, J., LEWIS, C., TORNER, J., GUERMAZI, A., ROEMER, F., MCCULLOCH, C. & FELSON, D. T. 2011. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis Rheum*, 63, 691-9.
- ZHAO, L. J., JIANG, H., PAPASIAN, C. J., MAULIK, D., DREES, B., HAMILTON, J. & DENG, H. W. 2008. Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis. *J Bone Miner Res*, 23, 17-29.
- ZHAO, L. J., LIU, Y. J., LIU, P. Y., HAMILTON, J., RECKER, R. R. & DENG, H. W. 2007. Relationship of obesity with osteoporosis. *J Clin Endocrinol Metab*, 92, 1640-6.